or without androstenedione and L-cysteine at 37 °C with the placental microsomes (1 mg of protein), 600 μ M NADPH, and MeOH (50 μ L) in 67 mM phosphate buffer, pH 7.5, in a total volume of 1 mL in air or N₂ atmosphere. Aliquots (50 μ L), in duplicate, were removed at various time periods (0–12 min) and added to a solution of [1 β -³H]androstenedione (1 μ M, 3.0 × 10⁵ dpm), NADPH (180 μ M) in 67 mM phosphate buffer, pH 7.5 (total

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Syntheses of Tolrestat Analogues Containing Additional Substituents in the Ring and Their Evaluation as Aldose Reductase Inhibitors. Identification of Potent, Orally Active 2-Fluoro Derivatives

Jay Wrobel,* Jane Millen,[†] Janet Sredy, Arlene Dietrich, Beverly J. Gorham, Michael Malamas, Joseph M. Kelly, John G. Bauman, Maria C. Harrison, Linda R. Jones, Charles Guinosso, and Kazimir Sestanj

Wyeth-Ayerst Research, Inc., CN 8000, Princeton, New Jersey 08543-8000. Received January 11, 1991

A series of aldose reductase inhibitors were prepared which were analogues of the potent, orally active inhibitor tolrestat (1). These compounds (5, 7, 9, and 10) have an extra substituent on one of the unoccupied positions on the naphthalene ring of 1. Primary amide prodrugs of several members from the series 5 and 7, namely 6 and 8, respectively, were also prepared. These compounds were evaluated in two in vitro systems: an isolated enzyme preparation from bovine lens to assess their intrinsic inhibitory activity and an isolated sciatic nerve assay to determine their ability to penetrate membranes of nerve tissue. These compounds were also evaluated in vivo as inhibitors of galactitol accumulation in the lens, sciatic nerve, and diaphragm of galactose-fed rats. In general, compounds in series 5, 7, 9, and 10 were potent inhibitors of bovine lens aldose reductase. 2-Halo-substituted analogues from the series 5, 7, and 9 exhibited high activity in the nerve of the 4-day-galactose-fed rat, and in several instances, the primary amide prodrug 8 enhanced the in vivo potency of the respective carboxylic acid 7. Two 2-fluoro-derivatives, 8a and 9a, had especially high activity in vivo and were chosen for additional studies. These compounds were found to be approximately equipotent to tolrestat in the sciatic nerve of the galactose-fed rat and the STZ rat, as judged by their ED₅₀'s in these assays. Although primary amide analogue 8a did not have intrinsic inhibitory activity toward aldose reductase, it was metabolized to an active form in vivo and also in vitro within the sciatic nerve.

Introduction

Tolrestat¹ (1) is an orally effective aldose reductase inhibitor which is currently marketed under the tradename Alredase for the treatment of diabetic complications.^{2,3} The naphthoylamide analogue of tolrestat, 2,^{3a} and the 5-bromo bioisostere, 3,^{3a} were also shown to be potent aldose reductase inhibitors, although both compounds were somewhat less active in vivo than tolrestat. In addition, the *N*-carbomethoxy derivative 4,⁴ was recently shown to have similar potency to 2. Tolrestat and its analogues belong to the carboxylic acid class of aldose reductase inhibitors. The phthalazine acetic acids, ponalrestat^{3d} and zopalrestat,^{3e} are other members in this class reported to show good activity in vivo. Sorbinil² is the prototypical example for the other major structural class, the fivemembered ring cyclic imides.

Our earlier studies demonstrated that the intrinsic and oral activities of analogues of 1 were strongly influenced by the nature and position of the substituents on the naphthalene ring. Optimal activity in vivo was associated with 6-methoxy-5-(trifluoromethyl) substitution. As one aspect of our program to identify new aldose reductase inhibitors, we further explored the scope of these substituent effects. In this regard, we synthesized derivatives of 1-4, represented by 5, 7, 9, and 10, in which an extra substituent was added to one of the unoccupied positions on the naphthalene ring.

We had also previously shown that the carboxylic acid moiety in 1-4 was a key pharmacophore.^{3a,4} Alteration of



Sorbinil

this group by, for instance, esterification or amidation resulted in intrinsically inactive compounds. However,

[†]Current address: Department of Medicinal Chemistry and Natural Products, University of North Carolina, Chapel Hill, NC 27599-7360.

Sestanj, K.; Bellini, F.; Fung, S.; Abraham, N.; Treasurywala, A.; Humber, L.; Simard-Duquesne, N.; Dvornik, D. J. Med. Chem. 1984, 27, 255.

Scheme I^a



^aMethod A = Br₂/HOAc; method B = CuCl/DMSO/ Δ ; method C = I₂/HIO₃/H₂SO₄/HOAc/H₂O/60 °C; method D = CF₃CO₂Na/CuI/NMP/ Δ ; method E = fuming HNO₃/Ac₂O/5 °C; method E' = concentrated HNO₃; method F = H₂/Pd-C/EtOAc; method G = NaNO₂/HF-pyridine/-60 to 65 °C.

these ester and amide derivatives, particularly primary amides of compounds 1 and 2,^{3b,c} showed appreciable oral activity and therefore were probably functioning as pro-

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drugs. These findings encouraged us to prepare a number of primary amides of 5 and 7, namely 6 and 8 respectively.



Chemistry

Our target compounds were diversely substituted naphthoic acid derivatives that required different synthetic procedures for their preparation (Schemes I–IX). In general, these tolrestat analogues were prepared by amidation and amide side chain elaboration of the corresponding di- or trisubstituted naphthoic acids (Schemes VII and VIII). The naphthoic acids, in turn, were synthesized by several different methods (Schemes I–VI). For the preparation of several 2-alkyl-substituted analogues, Meyers' oxazoline chemistry⁵ was utilized. In these instances, the required sarcosine side chain was constructed from the oxazoline ring (Scheme IX).

2-Halo, 2-(trifluoromethyl), 2-alkoxy, 2-(methylthio), and 4-fluoronaphthoic acids were prepared from the known naphthalene derivative 11⁶ (Schemes I and II). Bromi-

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Scheme II^a



^a Method H = (1) NBS/(PhCO₂)₂/CCl₄, Δ , (2) HCO₂Na/EtOH/H₂O/ Δ , (3) aq NaOH, (4) Jones oxidation; method I = NaH/ROH/CuI/THF/ Δ ; method J = KOtBu/CH₃SH/Cu₂O/DMF/ Δ .

Scheme III^a



°Method K = NaClO₂/resorcinol/tBuOH/dioxane/HOAc/ Δ ; method L = CH₃I/EtiPr₂N/CH₂Cl₂; method M = (1) nPrSH/NaH/DMF/60 °C; (2) PhCH₂Br/K₂CO₃/DMF. ^bSee footnotes in Scheme I. ^cSee footnotes in Scheme VI.

nation of 11 led to 12^7 (method A, Scheme I, 98%), which underwent chlorine substitution to 13 upon reaction with CuCl in DMSO⁸ (method B, 100%). A second trifluoromethyl substituent (compound 15) was introduced by iodination of 11 (method C, 64%) followed by reaction of iodide 14 with sodium trifluoroacetate and CuI^{7,9} (method D, 73%).

2- and 4-fluoro derivatives 20 and 21 were prepared from 11 via a three-step sequence. Reaction of 11 with concentrated HNO₃ (method E') provided a 45:55 mixture of nitro compounds 16 and 17 which were readily separated chromatographically. The selectivity for 16 (\sim 5:1) could be greatly improved by treating 11 with fuming HNO₃ in acetic anhydride.¹⁰ Compound 16 was selectively crystallized from the crude reaction mixture in 40–50% yields. Reduction of 16 or 17 using Pd–C-catalyzed hydrogenation afforded amines 18 and 19, respectively (method F, 95%). One-pot diazotization and fluorine displacement could be effected in good yields with either amine by using the Olah procedure (NaNO₂ in HF-pyridine)¹¹ to provide fluorides 20 and 21 (method G, 60–80%).

The halo and (trifluoromethyl)naphthalenes 12, 13, 15, 20, and 21 were converted to their naphthoic acid derivatives (22-26, respectively, Scheme II) by oxidation of the 1-methyl moiety employing a four-step/three-pot sequence involving benzylic bromination with NBS, hydroxide displacement on the resultant bromide and Jones oxidation

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Scheme IV^a



°Method N = (1) SBuLi/TMEDA/THF/-78 °C, (2) DMF/-78 to 25 °C, (3) NaBH₄/EtOH, (4) pTSA/PhCH₃/ Δ ; method O = (1) nPrSH/NaH/DMF/70 °C, (2) Raney Ni/EtOH/H₂O; method P = (1) sBuLi/TMEDA/THF/-78 °C, (2) PhCHO/-78 to 25 °C, (3) $pTSA/PhCH_3/\Delta$; method Q = $H_2/Pd-C/HOAc/95$ °C.

(method H, $\sim 70\%$ overall). 2-Alkoxy- and 2-(methylthio)naphthoic acids 27 and 28 were then obtained by copper(I)-mediated reaction of 2-bromo acid 22 with sodium alkoxides or potassium methylmercaptide (methods) I and J, respectively, 70-90%).¹²

2-Alkoxy-1-naphthoic acids were also be prepared from 2,5-dimethoxy-1-naphthaldehyde 2913 (Scheme III). Oxidation of 29 with sodium chlorite¹⁴ provided 2,6-dimethoxy-1-naphthoic acid 30 in 82% yield (method K). Other oxidation methods ($KMnO_4$, Jones oxidation) caused extensive decomposition of 29. The 2-(benzyloxy) substituent was introduced by selective demethylation of 29 at the 2-position using sodium propanethiolate in DMF,¹⁵ followed by reaction of the 2-hydroxyaldehyde with benzylbromide and base (method M, 69%). Chlorite oxidation provided the corresponding 2-(benzyloxy)-1-naphthoic acid 31.

2-Methyl and 2-benzyl analogues were prepared by employing ortho-lithiation technology^{16,17} (Scheme IV). Reaction of 6-methoxy-1-naphthoic acid diethylamide $(33)^{17}$ with sec-butyllithium-TMEDA and quenching the resultant lithio species with DMF led to the 2-formyl derivative which was reduced with NaBH₄ to the alcohol and cyclized (catalytic pTSA in toluene) to γ -lactone 34 (method N, 70%). Similarly, reaction of the 2-lithio derivative of 33 with benzaldehyde, followed by cyclization, provided phenyl-substituted lactone 35 (method P, 85%). Sodium propanethiolate¹⁵ opening of lactone 34, then Raney nickel desulfurization led to 2-methyl-1-naphthoic acid 36 (method O, 47%). The 2-benzyl counterpart 37 was prepared via hydrogenolysis of the benzylic C-O bond of 35 (method **Q**, 92%).

3-, 4-, and 7-substituted naphthoic acids were most conveniently prepared from the appropriately substituted cinnamaldehydes 42, 45, and 47 according to the methods in Scheme VI. These cinnamaldehyde starting materials

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were prepared by a variety of methods shown in Scheme V. 3-Methoxybenzaldehyde 41 was condensed with an alkyl or aralkylaldehyde (40c-f) by using KOH in ethanol to afford 42c-f (method T, 60-80%). Aldehyde 40f was not commercially available but was readily prepared from the benzyl bromide 38 (methods R and S). α -Fluoro analogue 42a was synthesized via a three-step sequence¹⁸ involving condensation of ethyl fluoroacetate and 41, followed by LiAlH₄ reduction of the resultant enoate to the allylic alcohol and oxidation of this alcohol to 42a using MnO_2 (method T', 40%). Bromination and dehydrobromination¹⁹ of 3-(3-methoxyphenyl)propenal 43²⁰ provided α -bromo derivative 42b in 43% yield. 3-Methoxy-4-methylbenzaldehyde (44)²¹ and phenylacetophenone 46 (the latter was prepared from aldehyde 41 and benzyl Grignard reagent, then Jones oxidation, method W) were converted to substituted cinnamaldehydes 45 and 47, respectively, via standard Horner-Emmons conditions, followed by ester to aldehyde functional group conversion (method V, 60-70%).

Referring to Scheme VI, aldehydes 42, 45, and 47 were condensed with the sodium salt of triethyl 2-ethoxyphosphonoacetate²² (method X^{23}) and the resultant 2ethoxy dienoate 48 was cyclized by action of catalytic *p*-toluenesulfonic acid to the naphthoic acid ethyl ester 49 (method Y,²³ ~60% from the corresponding cinnamaldehyde). Bromination, followed by saponification or, alternatively, bromination followed by trifluoromethylation and saponification, led to 3-, 4-, or 7-substituted-5-bromo or 5-(trifluoromethyl)-6-methoxynaphthoic acids 52a-i.

The 1-naphthoic acids 22-28, 30, 31, 36, 37, and 52a-i were converted to tolrestat analogues in the following manner (Scheme VII). Reaction of 22-28 and 52 with sarcosine methyl ester under standard amidation conditions (methods AA, AA', or AA") afforded the naphthoylsarcosine methyl esters 53. For compounds 30, 31,

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Scheme V^a



° Method R = (1) $CH_2(CO_2Me)_2/NaH/THF$, (2) $KOH/THF/H_2O/\Delta$, (3) HCl/H_2O , (4) $xylenes/\Delta$; method S = (1) BH_3 'THF, (2) PCC/CH_2Cl_2 ; method T = KOH/EtOH/0 °C; method T' = (1) $FCH_2O_2Et/NaH/EtOH/Et_2O$, (2) $LiAlH_4/Et_2O$, (3) MnO_2/Et_2O ; method U = (1) $Br_2/HOAc/0$ °C, (2) $K_2CO_3/0$ to 100 °C; method V = (1) $(Et_2O)_2POCH_2CO_2Et/NaH/PhCH_3/THF$, (2) $DIBAL/Et_2O/-78$ °C, (3) PCC/CH_2Cl_2 ; method W = (1) $PhCH_2MgCl/THF/-78$ °C, (2) Jones oxidation.

36, and 37, the 5-trifluoromethyl substituent was introduced after the amidation (method AA) using previously mentioned procedures (methods A and D). Ester hydrolysis of 53 (method Z) led to targets 7. Primary amide derivatives 8 were obtained from ester 53 or acid 7 by using standard methods (BB, CC, or CC'). Reaction of 7 with N-(ethoxycarbonyl)-N-tert-butylcarbodiimide²⁴ provided ethyl carbamate 54 (method DD, 50%).

Naphthoylthioamide methyl esters 55 were prepared from the corresponding naphthoylamides 53 with Lawesson's reagent²⁵ (method EE) or P_4S_{10} -pyridine (method EE'). Naphthoylamides with bulky, electron-withdrawing 2-substituents, i.e., 2-Br or 2-CF₃, did not react with either reagent. However the naphthoylamides with electron-releasing 2-substituents, even sterically demanding ones such as 2-OPh and 2-OCH₂Ph, were successfully converted to naphthoylthioamides 55. Ester saponification (method Z) led to tolrestat analogues 5. Primary amide derivatives 6 were synthesized from 5 or 55 by the methods described above.

N-Carbalkoxytolrestat analogues related to 4 were prepared as outlined in Scheme VIII from naphthoic acids 22, 23, 25, 27e, 33, or 52b. Reaction of these acids with the Mitsunobu carbodiimide²⁴ (method DD) led to *N*naphthoylcarbamate 56. Compounds 56 were also obtained via base-promoted acylation of the primary naphthamides with ethyl or methyl chloroformate (method DD, 50–60%) or by conversion of these amides to the acyl isocyanate using oxalyl chloride followed by treatment with ethanol or methanol (method DD",²⁶ 50–60%). N-Alkylation of 56 with *tert*-butyl bromoacetate (method FF, 75–85%) provided 58. Targets 9 and 10 were then obtained upon treatment of 58 with formic acid to removed the *tert*-butyl moiety (method II, 75–95%).

Alternatively, 58 was synthesized from naphthoylglycine ester 57 by N-acylation using ethyl or methyl chloroformate (methods HH, 70–80%). Precursor 57 was obtained from the corresponding naphthoic acid under standard amidation conditions (methods GG or GG'). Naphthoylglycine benzyl esters 59 were prepared from the naphthoic acid and glycine benzyl ester under standard amide-forming conditions followed by N-acylation of the resultant secondary amide with ethyl or methyl chloroformate (method JJ). Hydrogenolysis of 59 led to 9 or 10. Primary amide 60 was made from 9a in the usual manner (method CC') and alkylation of 9a with chloro N,N-diethylacetamide provided glycolate diethylamide²⁷ 61 (method KK, 72%).

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Scheme VI^a



528 Y = Br, R = 3-F; **520** Y = Br, R = 3-Br; **520** Y = Br, R = 3-CH₃; **520** Y = Br, R = 3-Ph **52e** Y = Br, R = 3-CH₂Ph; **52f** Y = CF₃, R = 3-Ph; **52g** Y = Br, R = 4-CH₂Ph, **52h** X = Br, R = 7-CH₃; **52i** Y = Br, R = 3- CH₂

^a Method X = $(EtO)_2POCH(OEt)CO_2Et/NaH/DMF$; method Y = $I_2/pTSA/PhCH_3/\Delta$; method Z = NaOH/H₂O/THF/EtOH. ^bSee footnotes for Scheme I.

In instances where the Meyers' oxazoline methods⁵ were used to prepare 2-alkyl analogues (Scheme IX), hydrolysis of the resulting oxazolines to 2-alkylnaphthoic acids was difficult due to the hindered environment of the oxazoline moiety. Instead, the oxazoline, resulting from organolithium displacement of methoxide on 62, was Nmethylated²⁸ with methyl iodide and then the oxazoline ring was opened to the N-methyl-N-naphthoylethanolamine acetate upon treatment with Hunig's base and acetic acid.²⁹ Aromatic bromination provided 63 (method MM, 30% overall). Trifluoromethylation of 63, followed by base-promoted acetate hydrolysis and Jones oxidation of the resultant primary alcohol (method NN) led to 2-alkyloxotolrestat analogues 70 and 7n. Chemical data and synthesis route information (by method letters) for the individual target compounds are compiled in Table I.

Biological Results and Discussion

Two in vitro systems were used to evaluate the target compounds as inhibitors of aldose reductase. The intrinsic activity of each compound was assessed by measuring the inhibition of enzymatic activity in a partially purified bovine lens preparation. Because aldose reductase is an intracellular enzyme, the ability of the inhibitor to penetrate the membranes of the target tissue is also an important component of its biological activity. This parameter was therefore evaluated by measuring the inhibition of sorbitol accumulation in rat sciatic nerves incubated in the presence of excess glucose. Finally, the compounds were evaluated in vivo as inhibitors of galactitol accumulation in the lens, sciatic nerve, and diaphragm of galactose-fed rats. The nerve and lens were evaluated because they are therapeutic targets. The diaphragm, although not a therapeutic target, was also evaluated because it accumulates polyol (3 μ g of galactitol/mg wet weight) and is highly vascular, thus allowing the assessment of a compound in a tissue where there is optimal distribution. The results of the biological evaluations are given in Table II.

In general, analogues 5, 7, 9, and 10 were potent inhibitors of aldose reductase, comparable to tolrestat (1) in the isolated enzyme preparation ($\geq 60\%$ at 10^{-7} M). Notable exceptions included 7-substituted compounds 5p and 7w and several analogues possessing sterically large or branched-chain 2-alkyl substituents (7d,n,o) or 2-alkoxy moieties (7g,h). The low activities exhibited by these compounds were probably due to a decreased ability to

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Scheme VII^a



° Method AA = (1) $(COCl)_2/DMF/CH_2Cl_2$, (2) $CH_3NHCH_2CO_2CH_3\cdot HCl/TEA/THF$; method AA' = (1) $Me_2N(CH_2)_3N=C=NEt\cdot HCl/HOBT/DMF$, (2) $CH_3NHCH_2CO_2CH_3\cdot HCl/TEA$; method AA'' = (1) $SOCl_2/DMF/CH_2Cl_2$, (2) $CH_3NHCH_2CO_2CH_3\cdot HCl/TEA$; method BB = $NH_3/THF/MeOH$; method CC = (1) $Me_2N(CH_2)_3N=C=NEt\cdot HCl/HOBT/DMF$, (2) NH_3/THF ; method CC = (1) $(COCl)_2/DMF/THF$, (2) NH_3/THF ; method DD = $tBuN=C=NCO_2Et/THF/D$; method EE = Lawesson's reagent/PhCH₃/ Δ ; method EE' = $P_4S_{10}/pyridine/\Delta$. ^b See footnotes in Scheme I. ^c See footnotes in Scheme VI.

Scheme VIII^a



°Method DD' = (1) SOCl₂/DMF, (2) NH₄OH/THF/0 °C, (3) NaH/THF, (4) ClCO₂R'/THF; method DD'' = (1) SOCl₂/DMF, (2) NH₄OH/THF/0 °C, (3) (COCl)₂/(CH₂Cl)₂/ Δ , (4) R'OH/PhH/ Δ ; method FF = (1) NaH/THF, (2) BrCH₂CO₂tBu·HCl/THF, 60 °C; method GG = (1) (COCl)₂/DMF/CH₂Cl₂, (2) NH₂CH₂CO₂tBu·HCl/TEA/THF; method GG' = (1) Me₂N(CH₂)₃N=C=NEt·HCl/HOBT/DMF, (2) NH₂CH₂CO₂tBu·HCl/TEA; method HH = (1) NaH/THF/60 °C, (2) ClCO₂R'/THF; method II = HCO₂H; method JI = (1) (COCl)₂/DMF/THF, (2) NH₂CH₂CO₂CH₂Ph, (3) LDA/THF/-78 °C, (4) ClCO₂R'/-78 to 25 °C; method KK = ClCH₂CONEt₂/K₂CO₃/DMF. ^bSee footnotes in Scheme VII.

Scheme IX^a



^aMethod LL = (1) (COCl)₂/DMF/THF, (2) NH₂CH₂CH₂OH, (3) SOCl₂; method MM = RLi or RMgCl/THF/-40 °C, (2) CH₃I, (3) EtiPr₂N/HOAc/EtOAc, (4) Br₂/HOAc; method NN = Jones oxidation. ^bSee footnotes in Scheme I. ^cSee footnotes in Scheme VI.

interact with the enzyme because of steric effects. Compounds in the thionaphthoylamide series (5) showed slightly higher inhibitory values than their naphthoylamide counterparts (7), a trend that has been observed previously.⁴ The amide derivatives 6, 8, 54, and 60 and ester analogues 53 and 61 were not active in this in vitro assay at 10^{-5} M, the highest dose tested, corraborating our previous in vitro findings.^{3b} However, many of these compounds were active in vivo, and therefore, were probably functioning as prodrugs (vide infra).

Consistent with our previous studies,⁴ we found that in vitro inhibitory activity of 5, 7, 9, or 10 in the isolated sciatic nerve did not always predict oral activity in the galactose fed rat model. Although isolated nerve values $\geq 60\%$ at 10⁻⁵ M and $\geq 30\%$ at 10⁻⁶ M appeared to be necessary for good potency in vivo, there were many examples of analogues with strong activity in this assay that were devoid of any oral effects. For example 7t caused a 63% decrease in in vitro sciatic nerve sorbitol accumulation at 10⁻⁶ M, which is similar to the value exhibited by tolrestat (1), yet this compound was inactive in vivo. While it is obvious that the inhibitor must possess some ability to cross biological membranes, high activity in this regard did not guarantee oral potency, and other factors including absorption, distribution, and metabolism also strongly influenced oral efficacy.

The target compounds (5-10) were most readily distinguished by their potency in vivo (galactose-fed rat model). In the thionaphthoylamide (5) and naphthoylamide (7)series, compounds with 2-halo substituents (i.e., 5a, 7a, 7b) or 2-(lower)alkoxy moieties (i.e., 5d,g, 7f,g,k) showed the most promising results, exhibiting significant inhibition of galactitol accumulation in the sciatic nerve at reasonably low doses ($\leq 50 \text{ mg/kg}$ per day). Also, within these two series, naphthoylamide 7 was generally equally effective in the nerve when compared to the respective thionaphthoylamide congener 5. For example, compare 5a with 7a, 5b with 7b, and 5g with 7k. These results differed from previous studies in which the thioamide analogue was always superior to the amide in vivo.^{3,4} Another comparison demonstrated that 2-halo and 2-(lower)alkoxy derivatives of 7 had superior in vitro and in vivo profiles over the hydrogen substituted analogue oxotolrestat (2) (compare 2 with 7a, 7b, 7f, and 7k). Methyl naphthoylcarbamates 9 containing 2-halo substituents also showed

significant activity in the nerve at doses $\leq 50 \text{ mg/kg}$ per day. Also, these carbamates were superior in oral activity over their ethyl carbamate counterparts 10, and over the hydrogen substituted congener 4.

Several primary amide prodrugs of thionaphthoylamide series 5 and naphthoylamide series 7 were prepared. These were compounds in series 6 and 8, respectively. In several instances oral activity in the nerve improved with the primary amide derivative (compare 7a with 8a, and 7b with 8b). Also, increased potency in vivo was observed in the one instance in which an ethyl carbamate prodrug was used (compare 7a with 54). On the other hand, ester prodrugs of 7a (53) and 9a (61) and the primary amide prodrug of 9a (60) did not result in increased in vivo potency.

Oral activity was best demonstrated by the members of the series 5-10 that contained a 2-fluoro substituent (including 5a, 6a, 7a, 8a, 9a, 10a, and 54). Two of these, primary amide prodrug 8a and methyl carbamate 9a, appeared to have potency equivalent to that of tolrestat (1) and were therefore evaluated more extensively.



The comparative in vivo and in vitro data for 8a, 9a, and tolrestat are shown in Tables III and IV. ED_{50} values (Table III) for the inhibition of galactitol accumulation in the sciatic nerve and red blood cell (RBC) of the galactose-fed rat were determined. In addition, ED_{50} values in another in vivo model, the 2-week-streptozocin-diabetic rat (STZ), were also obtained. In this model the compound's ability to inhibit sorbitol accumulation in the sciatic nerve of the STZ rat was measured. IC₅₀ values (Table IV) were also determined for 8a, 9a, and tolrestat in the bovine lens aldose reductase preparation and isolated sciatic nerve. Furthermore IC₅₀ values for the inhibition of sorbitol accumulation in isolated lens cells and RBC were determined.

Table I. Chemical Data



									purification method ^e
no.	R	R′	Х	Y	Z	formulaª	synthesis route ^b	mp, °C	(solvent)
5a	2-F	CH ₃	S	CF ₃	OH	C16H13FANO3S	E, F, G, H, AA, EE, Z	179-190 dec	I (EtOH/H ₂ O)
5b	2-C1	CH ₃	S	CF,	OH	C ₁₆ H ₁₃ ClF ₃ NO ₃ S	A, B, H, AA', EE, Z	164-166	II (hexane)
5c	2-OMe	CH ₃	S	CF_3	ОН	$C_{17}H_{16}F_3NO_4S$	K, AA, A, D, EE, Z	162-164	I (hexane/toluene)
5 d	2-OEt	CH ₃	S	CF_3	он	$C_{18}H_{18}F_3NO_4S$	A, H, I, AA', EE, Z	180-182	I (petroleum ether/CHCl ₃)
5e	2-OPh	CH_3	S	CF_3	он	$C_{22}H_{18}F_3NO_4S$	A, H, I, AA', EE, Z	112-132 dec	I (hexane/CHCl ₃)
5f	2-OCH ₂ Ph	CH ₃	S	CF ₃	OH	$C_{23}H_{20}F_3NO_4S$	M, K, AA, A, D, EE, Z	190-195	I (EtOH)
5g	$2 - OCH_2 CF_3$	CH ₃	S	CF ₃	OH	$C_{18}H_{15}F_6NO_4S$	A, H, I, AA', EE, Z N, O , AA, A, D, FF, Z	194-196	I (CHCl ₃)
5 D	2-CH ₃		2		0H	C H D-FNOS	N, U, AA, A, D, EE, Z TV V V A 7 AA// FF 7	1/0-1/9	I (nexane/toluene) I (iP-OH/H O)
51 51	3-F	CH.	S	Br Br	0H 0H	C.H.Br.NO.S	$\begin{array}{c} \mathbf{I}, \mathbf{X}, \mathbf{I}, \mathbf{A}, \mathbf{Z}, \mathbf{A}\mathbf{A}, \mathbf{E}\mathbf{E}, \mathbf{Z} \\ \mathbf{I} \mathbf{X} \mathbf{V} \mathbf{A} \mathbf{Z} \mathbf{A}\mathbf{A}' \mathbf{E}\mathbf{E} \mathbf{Z} \end{array}$	205-207	$\frac{1}{(111011/1120)}$
•,	0-101	QIII3	2	5.	011	015111301211030	0, 11, 1, 11, 2, 121, 22, 2	200 201	then II (hexanes)
5 k	3-CH ₃	CH ₃	S	Br	OH	C16H16BrNO3S	T, X, Y, A, Z, AA", EE, Z	21 9 -221	I (Et ₂ O/CHCl ₃)
51	3-Ph	CH ₃	S	Br	OH	C ₂₁ H ₁₈ BrNO ₃ S	T, X, Y, A, Z, AA", EE', Z	142-144	III (99:1 $CH_2Cl_2/MeOH)^{e}$
5m	3-Ph	CH3	S	CF_3	ОН	$C_{22}H_{18}F_3NO_3S$	T, X, Y, A, D, Z, AA", EE', Z	186-188.5	III (9:1 CH ₂ Cl ₂ /CH ₃ CN) ^e
5n	3-CH ₂ Ph	CH3	S	Br	OH	$C_{22}H_{20}BrNO_3S$	T, X, Y, A, Z, AA", EE, Z	156-158	I (acetone/Et ₂ O/hexane/ -20 °C)
50	4-F	CH ₃	S	CF ₃	OH	$C_{16}H_{13}F_4NO_3S$	E', F, G, H, AA, EE, Z	174-176	$I (EtOH/H_2O)$ I (Et O (herease (0.8C))
op 6e	7-CH3	CH ₃	2	DI		$C_{16}\Pi_{16}\Pi_{16}\Pi_{10}$	V, A, I, A, A, AA, EE, A F F C H AA FF 7 CC	210 QCC	$I (E_{2}O/nexame/0 C)$
6h	2-r 3-CH	CH.	ŝ	Br	NH.	$C_{16}H_{14}F_4N_2O_2S$ $C_{16}H_{14}F_4N_2O_2S$	T X V A Z AA" EE Z	113-115	III (1.4 herene/CH-Cl.)
	0.0113	0113	2	2.	1112	016117251102020	1, 11, 1, 11, D, 111 , DD, D	110 110	then II (hexanes)
7a	2-F	CH ₃	0	CF ₃	OH	C ₁₆ H ₁₃ F ₄ NO ₄	E, F, G, H, AA, Z	160-161	I (EtOH)
7b	2-Cl	CH ₃	0	CF_3	OH	C ₁₆ H ₁₃ ClF ₃ NO ₄	A, B, H, AA', Z	157-159	I (petroleum ether/CHCl ₃)
7c	2-Br	CH_3	0	CF ₃	ОН	C ₁₆ H ₁₃ BrF ₃ NO ₄	A, H, AA', Z	163.5-165	I (1:1 hexane/CHCl ₃)
7d	2-CF ₃	CH3	0	CF ₃	OH	$C_{17}H_{13}F_6NO_4$	C, D, H, AA", Z	189-191	I (hexane/CHCl ₃)
7e	2-OMe	CH ₃	0	CF3	OH	$C_{17}H_{16}F_3NO_5$	K, AA, A, D, Z	195-197	I (hexane/CH2Cl2) $I (From (H, O))$
11 7a	2-0Et 2 On Pr		Ň	CF3	0H 0H		$\begin{array}{c} \mathbf{A}, \mathbf{\Pi}, \mathbf{I}, \mathbf{A}\mathbf{A}', \mathbf{Z} \\ \mathbf{A}, \mathbf{U}, \mathbf{I}, \mathbf{A}\mathbf{A}', \mathbf{Z} \end{array}$	100-170	$I(EtOH/H_2O)$
7h	2-0nBu	CH ₃	ŏ	CF.	OH	C ₁₉ H ₂₀ F ₃ NO ₅	A. H. I. AA'. Z	150-155	II (petroleum ether)
7i	2-OPh	ČH,	ŏ	CF.	ŎĦ	$C_{22}H_{12}F_{3}NO_{5}$	A, H, I, AA', Z	180-182	$I (EtOH/H_{2}O)$
7j	2-OCH ₂ Ph	CH ₃	0	CF_3	OH	$C_{23}H_{20}F_3NO_5$	M, K, AA, A, D, Z	174-175	I (EtOH)
7k	2-OCH ₂ CF ₃	CH3	0	CF_3	он	C ₁₈ H ₁₅ F ₆ NO ₅	A, H, I, AA', Z	158-160	I (hexane/CHCl ₃)
71	2-SMe	CH3	0	CF ₃	OH	$C_{17}H_{16}F_3NO_4S$	A, H, J, AA", Z	190-191	I (2:1 hexane/CHCl ₃)
7m	$2 - CH_2 Ph$	CH ₃	0	CF3	OH	$C_{23}H_{20}F_3NO_4$	P, Q, AA, A, D, Z	202-203	$I (EtOH/H_2O)$ I (hereing (EtOA))
7B 70	2-nBu 2-tBu	CH.	0	CF.	OH OH	$C_{20}\Pi_{22}\Gamma_{3}NO_{4}$	K, LL, MM, D, Z, NN K LL, MM D, Z, NN	148-192	I (nexane/ btOAc) III (5.1 CH.CL. /EtOAc)
10	2-000	0113	v	013	011	02011221 31404	11, <u>DD</u> , MMI, <u>D</u> , <u>D</u> , 1111	100 104	then II (bexane/EtOAc)
7p	3-CH ₃	CH ₃	0	Br	ОН	C16H16BrNO4	T, X, Y, A, Z, AA", Z	195-196	$I (MeOH/H_2O)$
7q	3-Ph	CH ₃	0	Br	ОН	C ₂₁ H ₁₈ BrNO ₄	T, X, Y, A, Z, AA", Z	208-210	$I (MeOH/H_2O)$
7 r	3-Ph	CH3	0	CF_3	ОН	$C_{22}H_{18}F_{3}NO_{4}$	T, X, Y, A, D, Z, AA", Z	175-177	II (petroleum ether)
78	3-CH ₂ Ph	CH3	0	Br	OH	$C_{22}H_{20}BrNO_4$	T, X, Y, A, Z, AA', Z	160-162	I (CHCl ₃ /Et ₂ O/ -20 °C)
7t 7.,	g A F		Ň	BI	OH	$C_{22}H_{18}Br_2FNO_4$	$\mathbf{R}, \mathbf{S}, \mathbf{T}, \mathbf{X}, \mathbf{Y}, \mathbf{A}, \mathbf{Z}, \mathbf{A}\mathbf{A}^{\prime\prime}, \mathbf{Z}$	183-180	$I (acetone/H_2U)$ I (F+OH/H O)
7v	4-CH _a Ph	CH ₂	ŏ	Br	0H	CasHasBrNO.	W. V. X. Y. A. Z. AA'. Z	93-95	$I (CHCl_s/EtcO/hexane/-20 °C)$
7w	7-CH ₃	CH ₃	ŏ	Br	ŎĦ	C _{1e} H _{1e} BrNO ₄	V, X, Y, A, Z, AA', Z	141-143	$I (Et_{*}O - 20 °C)$
8 a	2-F	CH₃	0	CF_3	NH_2	$C_{16}H_{14}F_4N_2O_3$	E, F, G, H, AA, BB	171-173	II (petroleum ether/ Et_2O)
									then I (toluene)
8b	2-CI	CH ₃	0	CF ₃	NH_2	$C_{16}H_{14}CIF_3N_2O_3$	A, B, H, AA', BB	196-198	III (19:1 $CHCl_3/MeOH$)
8C	$2 \cdot 0 \circ H_2 \circ F_3$	CH ₃	0	CF ₃	\mathbf{NH}_2	$C_{18}H_{16}F_6N_2O_4$	А, Н, І, АА', ВВ	162-164	then I (horeno/CHCL)
84	2-nBu	CH.	0	CF.	NH.	C.H.F.N.O.	K LL MM D Z NN CC	156-158	I (3.2 herane/EtOAc)
8e	2-tBu	CH ₃	ŏ	CF ₃	NH ₂	$C_{20}H_{23}F_3N_2O_3$	K, LL, MM, D, Z, NN, CC	115-120	III (EtOAc) then II (hexane)
8 f	4-F	CH₃	0	CF ₃	NH_2	$C_{16}H_{14}F_4N_2O_3$	E', F, G, H, AA, BB	180-183	III (9:1 CHCl ₃ /MeOH)
9a	2-F	CO_2Me	0	CF_3	он	C ₁₇ H ₁₃ F ₄ NO ₆	E, F, G, H, GG, HH, II	158.5-160	II (petroleum ether/ Et_2O)
0L	0.01	00 M-	^	CE	OH I			160 165	then I (toluene/hexane)
90	2-01 2-Br		ň	CF.	0H	$C_{17}H_{13}CF_{3}NO_{6}$	A H DD' FF II	164-166	I (petroleum ether/CHCl.)
9d	2-OMe	CO ₂ Me	ŏ	CF ₃	ŎН	$C_{18}H_{18}F_{3}NO_{7}$	K, L, A, D, Z, JJ, F	175-177	II (hexane/EtOAc)
9e	2-OCH ₂ CF ₃	CO ₂ Me	0	CF_3	он	C ₁₉ H ₁₅ F ₆ NO ₇	A, H, I, GG', HH, II	186-187	I (CHCl _s)
10a	2-F	CO ₂ Et	0	CF ₃	он	$C_{18}H_{15}F_4NO_6$	E, F, G, H, DD, FF, II	135.5-138	I (petroleum ether/benzene)
100	2-CI	CO ₂ Et	0	CF3	OH	$C_{18}H_{15}CIF_3NO_6$	A, B, H, DD, FF, II		I (petroleum ether/benzene)
100	2-Dr 2-OCH-CF		ŏ	CF ₃	OH OH	$C_{18}H_{15}DFF_{3}NO_{6}$	A H I BB FF II	165 5-167	I (netroleum ether/CHCl _a)
10e	3-Br	CO ₂ Et	ŏ	Br	он	C ₁₇ H ₁₈ Br ₉ NO ₆	U. X. Y. A. Z. DD". FF. II	164-165	III (7:3 hexanes/EtOAc)*
		6 — -	-	-		21 - 10 - 2 0	, ., , ., .,, <u> ,</u>		then II (hexanes)
53	2-F	CH3	õ	CF ₃	OMe	C ₁₇ H ₁₅ F ₄ NO ₄	E, F, G, H, AA	112.5-114	I (petroleum ether/CHCl ₃)
54	2-F	CH3	0	CF ₃	NHCO ₂ Et	C ₁₉ H ₁₈ F ₄ N ₂ O ₅	E, F, G, H, AA, Z, DD	130-132	III (1:1 petroleum ether/Et ₂ O)
60	2-F	CO-Me	0	CF-	NH.	CurlluF.N.O.	E.F.G.H.GG HH II CC	199-202	I (netroleum ether/CHCl.)
61	2-F	CO ₂ Me	ŏ	ČF3	OCH2-	$C_{23}H_{24}F_4N_2O_7$	E, F, G, H, GG, HH, II, KK	104-107	II (hexane)
		•		5	CONEt ₂				

Footnotes to Table I

^aAnalyses (C, H, N) were within $\pm 0.4\%$ of theoretical values unless otherwise indicated. ^bSequential order of methods from Schemes I-IX. ^cI, Recrystallization; II, trituration; III, flash chromatography. ^dAnal. Calcd: H, 4.34. Found: H, 5.41. Exact mass (M + H) 372.08812, found 372.0879. ^cFlash chromatography performed with silica gel first treated with 2% H₃PO₄ in MeOH then dried in an oven. ^fAnal. Calcd: C, 54.99. Found: C, 54.58. Exact mass (M + H) 372.10587, found 372.10580. ^d _{3-CH₂} Br

Inhibitors 8a and 9a were equipotent to 1 in the sciatic nerve of the 4-day-galactose-fed rat; however 8a appeared to be slightly more potent in the nerve of the 2-weekstreptozotocin-diabetic rat than the other two compounds. Tolrestat, however had greater activity in the RBC than either 8a or 9a. The in vitro analyses (Table IV) revealed some interesting observations. While 9a was roughly similar to tolrestat in the various in vitro assays, compound 8a, because it is a prodrug, was expected to be inactive or very weakly active in all in vitro screens. Although this was the case for the partially purified enzyme preparation and the isolated lens and RBC assays, 8a had relatively good potency in the isolated sciatic nerve, comparable to that of 9a. Presumably 8a was metabolized to an active form, possibly the parent acid 7a, in this tissue.

Conclusions

Analogues, represented by 5, 7, 9, and 10, of aldose reductase inhibitors 1-4 were prepared. These new compounds have an extra substituent on one of the unoccupied positions on the naphthalene ring. Primary amide prodrugs of several members from the series 5 and 7, namely 6 and 8, respectively, were also prepared. With only a few exceptions, all compounds in series 5, 7, 9, and 10 were highly active as inhibitors of bovine lens aldose reductase. 2-Halo-, especially 2-fluoro-, substituted analogues from the series 5, 7, and 9 exhibited strong activity in the nerve of the 4-day-galactose-fed rat, and, as a departure to what was observed previously, the 2-halothionaphthoylamides (5a, 5b) were not superior in in vivo potency in the nerve relative to their naphthoylamide counterparts 7a and 7b. In several instances, the primary amide prodrug 8 enhanced the in vivo potency of the respective carboxylic acid 7. The best compounds in this study, 8a and 9a, were approximately equipotent to tolrestat in the sciatic nerve of the galactose-fed rat and the STZ rat, as judged by their ED_{50} 's in these assays. Compound 8a, although not an inhibitor of aldose reductase in vitro, can be metabolized to an active form in vivo and also within the sciatic nerve. The data presented here demonstrate that analogues 8a, 9a, and tolrestat, to date, remain among the most orally potent, carboxylic acid based aldose reductase inhibitors known.

Experimental Section

Partially Purified Enzyme Preparation. Previously described procedure was used.⁴

Isolated Tissues. Sciatic nerves, lenses, and erythrocytes (RBCs) were isolated from rats (Sprague–Dawley male, 200–250 g) and incubated with 5 or 50 mM glucose as previously described.⁴ All incubations were performed in triplicate.

Galactose Fed Rat Model. As previously described⁴ with the addition of RBC collection and analysis for polyol.

Streptozocin (STZ) Diabetic Rat Model. Sprague-Dawley male rats (Charles River, NY) weighing 200-250 g were used. Diabetes was induced by the iv injection of STZ (60 mg/kg, Sigma Chemical Co., St. Louis, MO) into the tail vein. STZ was dissolved in cold 0.03 M citrate buffer, pH 4.5. Plasma glucose concentrations were determined 2 days after STZ administration and at the termination of the study. Blood samples were drawn from the tail after a 4-h fast. Glucose was quantitated with a hexokinase procedure on an Abbott automated analyzer. Only animals which had plasma glucose levels >300 mg/dL at both time points were included in the study. Test compounds were suspended in 2% Tween 80 in saline and administered to individual groups of rats (n = 8-15) daily by gavage beginning on the day of STZ administration. Control diabetic rats (n = 8) received vehicle. All rats were maintained on normal rodent diet (Purina rodent chow 5001) with free access to food and water. After 2 weeks the rats were killed by decapitation and the sciatic nerves were removed and immediately frozen on porcelain plates on dry ice. Frozen tissues were homogenized in 5% trichloroacetic acid (TCA) and the deproteinized extracts were analyzed for sorbitol and as their aldonitrile acetate or acetate derivatives as previously described.³⁰

Statistical Analyses. In the in vitro tissue incubations and the in vivo studies (galactose fed and STZ diabetic rat models) all data are reported as mean values for three to eight drug-treated tissues samples. The Dunnett's multiple comparison test was used to assess the statistical significance between means of compound-treated tissues compared to the nontreated group. P <0.05 was statistically significant. Thus all percentage inhibition values given in the tables for each compound are statistically significant unless otherwise indicated.

Chemistry. Melting points were determined on an Electrothermal capillary melting point apparatus and are not corrected. Proton magnetic resonance (¹H NMR) spectra were recorded at 200 MHz (Varian XL-200), 400 MHz (Bruker AM-400), or 80 MHz (Varian CFT-20). Infrared spectra were obtained on either a Beckman Accu Lab 2 or a Perkin-Elmer Model 781 spectrophotometer as KBr pellets, thin films on sodium chloride plates, or solutions in chloroform and are reported in reciprocal centimeters (cm⁻¹). Mass spectra were recorded on either a Finnigan Model 8230 or a Hewlett-Packard Model 5995A spectrometer. Analyses (C, H, N) were carried out on a modified Perkin-Elmer Model 240 CHN analyzer. Analytical results for elements were within $\pm 0.4\%$ of the theoretical values. Flash chromatography was carried out according to the procedure of Still.³⁰ Thin-layer analyses were done on E. Merck silica gel 60 F-254 plates of 2.5-mm thickness

Method B. 2-Chloro-6-methoxy-1-methyl-5-(trifluoromethyl)naphthalene (13). Copper(I) chloride (35.78 g, 0.361 mol) was added to a solution of 2-bromo-6-methoxy-1-methyl-5-(trifluoromethyl)naphthalene $(12)^7$ (19.22 g, 0.0602 mol) in dry DMSO (194 mL) at room temperature under a dry N_2 atmosphere. The reaction mixture was heated at \sim 188 °C for 3 h, then cooled to room temperature and diluted with water (3 L). The resultant solids were collected and triturated well with EtOAc (2 L total). The triturates were combined, dried $(MgSO_4)$, and filtered, and the solvent was removed to give 13 as a white solid (16.7 g, 100%). A small sample was purified by flash chromatography (9:1 petroleum ether/CHCl₃) to give an analytically pure product: mp 102-103 °C; NMR (CDCl₃, 200 MHz) δ 2.72 (s, 3 H, CH₃), 3.99 $(s, 3 H, OCH_3), 7.34 (d, 1 H, J = 10 Hz, ArH), 7.48 (d, 1 H, J =$ 10 Hz, ArH), 7.98 (d, 1 H, J = 9 Hz, ArH), 8.17 (d, 1 H, J = 10Hz, ArH); IR (CHCl₃) 2950, 2858. Anal. (C₁₃H₁₀ClF₃O) C, H.

Method C. 2-Iodo-6-methoxy-1-methyl-5-(trifluoromethyl)naphthalene (14). A suspension of I_2 (22.28 g, 87.5 mmol), HIO₃ (5.74 g, 32.5 mmol), and 2-methoxy-5-methyl-1-(trifluoromethyl)naphthalene (11)⁶ (30.0 g, 125 mmol) in 80% HOAc (250 mL) and concentrated H₂SO₄ (1.5 mL) was heated to 60 °C under a dry N₂ atmosphere. After 5 h, more I₂ (9.52 g, 37.5 mmol) and HIO₃ (2.20 g, 12.5 mmol) were added. After 6 h, the reaction was cooled to room temperature and diluted with aqueous NaHSO₃ (2.5 L). The solid was collected by suction filtration and washed with aqueous NaHSO₃ (2 × 100 mL) and water (4 × 100 mL). The crude product was recyrstallized (ethanol) to provide 14 as a light pink solid (29.13 g, 64%): mp 129–130 °C; NMR (CDCl₃, 200 MHz) δ 2.85 (s, 3 H, ArCH₃), 3.99 (s, 3 H, ArOCH₃), 7.29 (d, 1 H, J = 9.9 Hz, ArH), 7.75 (d, 1 H,

⁽³⁰⁾ Kemper, C.; Dvornik, D. Proc. Soc. Exp. Biol. Med. 1986, 182, 505.

Table II. Bi	ological Dat	a
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	% aldose red	uctase inhibn in	vitro	aldose reductase inhibition in vivo			
	isolated	isolated sciatic nerve ^b		dose,	% in	hibn	
compd	10 ⁻⁷ M	10 ⁻⁵ M	10 ⁻⁶ M	per day	sciatic nerve ^c	diaphragm ^c	
5a	86	NT		25	92	93	
~1	•			5	NS	86	
5b	81	NT		24	NS	90	
5c	91	NT		26	NS	71	
5d	87	NT		28	46	85	
5e	89	NT		24	NS	83	
5f	84	NT		26	NS	80	
5g	86	NT		26	33	88	
5 h	70	NT		26	NS	91	
5 i	86	NT		26	NS	86	
5j	94	NT		26	NS	86	
5k	85	86	43	123	86	91	
				11	NS	48	
51	81	68	30	133	58	85	
5m	93	87	36	53	NS	82	
5n	84	78	48	144	46	84	
50	84	NT		25	94	90	
5n	8	NT		105	NS	34	
•₽	(53% at 10 ⁻⁶ M)			100	110		
				10	54	87	
6 a	NA	NT		5	33	80	
				2	NS	53	
6b	NA	NT		20	NS	NS	
				24	68	70	
79	80	66	41	20	62	72	
	00,			16	45	46	
7h	63	67	39	49	83	80	
	68	01	00	26	43	63	
70	69	67	27	20	40	84	
74	20	65	25	49	NS	59	
7u 7o		49	20	40	NG	NG	
76	62	40	20	40	110	110	
71	65	00 NUT	30	49	40	57	
/g	46	IN I NUT		50	48 NO	57	
/ n	42	N1 70	45	49	105	00	
71	83	78	45	48	32	67	
7)	73	NT		65	NS	23	
7 K	67	57	31	50	79	82	
				24	37	65	
71	69	60	41	50	NS	NS	
7 m	52	NT		50	NS	NS	
7 n	23	NT		94	NS	37	
70	6	NT		47	NS	NS	
	(23% at 10 ⁻⁶ M)						
7p	63	52	20	114	NS	NS	
7q	83	71	28	132	24	33	
7 r	63	77	32	50	NS	17	
7s	74	72	44	144	NS	24	
7t	66	92	63	52	NS	NS	
7u	64	NT		26	NS	15	
7v	80	NT		52	NS	34	
7w	20% at 10 ⁻⁵ M	NT		112	NS	NS	
				19	77	63	
8a.	NA	80	17	10	5 9	41	
				5	39	32	
8b	NA	NT		24	62	53	
8c	NA	NT		25	NS	NS	
8d	NA	NT		48	30	NS	
8e	NA	NT		48	NS	NS	
8 f	NA	NT		27	56	31	
0.0	96	61	20	14	72	74	
78	00	01	00	5	50	52	
9b	85	75	49	26	53	68	
9c	77	68	29	51	69	62	
9d	83	NT		49	36	33	
9e	83	64	36	27	NS	49	
10a	87	75	51	25	70	65	
				15	55	59	
10 b	79	79	54	50	NS	47	
10c	76	73	52	43	NS	24	
10 d	78	72	42	27	NS	39	
10e	84	NT		47	NS	NS	
53	NA	NT		27	48	48	

Table II (Continued)

	% aldose reduct	itro	aldose reductase inhibition in vivo			
	isolated	isolated sciatic nerve ^b		dose,	% inhibn	
compd	10 ⁻⁷ M	10 ⁻⁵ M	10 ⁻⁶ M	per day	sciatic nerve ^c	diaphragm ^c
				11	29	34
				22	80	55
54	NA	NT		10	59	41
				5	36	22
60	NA	34	4	16	NS	33
				11	NS	28
61	NA	NT		32	75	75
				11	39	36
1 (tolrestat)	65	82	61	6	53	80
2	57	74	27	75	56	27
-	0.			25	33	NS
				53	93	94
3	72	NT		25	64	90
-				18	39	88
4	82	58	NS	48	70	54
-	-			10	86	76
ponalrestat	$IC_{50} = 3.7 \times 10^{-6} M$	100	35	5	61	63
•	, ,	$(IC_{50} = 1.4 \times 10^{-6} M)$		$(ED_{50} = 4.0 \text{ mg/kg nerve})$		
zopalrestat	89	ŇŤ		10	70	80
•				5	NS	88
sorbinil	10	96	27	4	55	69
	$(IC_{50} = 1.1 \times 10^{-6} \text{ M})$	$(IC_{50} = 2.2 \times 10^{-6} \text{ M})$		$(ED_{so} = 4.2 \text{ mg/kg nerve})$		

^a Inhibition of enzymatic activity in partially purified bovine lens preparation (mean of two determinations). ^b Inhibition of sorbitol accumulation in rat sciatic nerves incubated in the presence of 50 mM glucose (n = 3). ^c Inhibition of galactical accumulation in the sciatic nerves or diaphragms of rats (n = 6) fed 20% galactose for 4 days; compounds were administered in the diet. All compounds were inactive or very weakly active in the lens at the given doses. NA = not active, no inhibitory activity at 10⁻⁶ M. NT = not tested. NS = no significant inhibition of polyol accumulation (p > 0.05).

Table III. Inhibition of Aldose Reductase in Vivo by 8a and 9a

	$ED_{50}, mg/kg$						
	galactose-fee	STZ rat ^b					
compd	sciatic nerve	RBC	sciatic nerve				
8a	5.5	8.5	<3°				
9a	4.8	3.5	4.0				
tolrestat	6.4	<2°	4.8				

^eInhibition of galactitol accumulation in the sciatic nerves or RBC of rats fed 20% galactose for 4 days; compounds were administered in the diet. All compounds had ED₅₀'s >100 mg/kg in the lens. ^bInhibition of sorbitol accumulation in the sciatic nerves of two week streptozotocin diabetic rat; compounds were administered daily by gavage. ^cLowest dose level examined.

Table IV. Inhibition of Aldose Reductase in Vitro by 8a and 9a

	$IC_{50} \times 10^8 M$							
	bovine	isolated tissue ^b						
compd	lens AR ^a	sciatic nerve	lens	RBC				
8a	inactive	310	>1000	1200				
9a	2.5	280	34	1.9				
tolrestat	3.4	54	100	1.5				

^a Inhibition of activity in a partially purified bovine lens preparation. ^bInhibition of sorbitol accumulation in rat sciatic nerves, lens, or RBC incubated in the presence of 50 mM glucose.

J = 9.8 Hz, ArH), 7.87 (d, 1 H, J = 9.6 Hz, ArH), 8.22 (d, 1 H, J = 9.5 Hz, ArH); MS (m/e) 366 (43), 129 (40), 82 (52), 69 (100). Anal. ($C_{13}H_{10}F_{3}IO$) C, H.

Method D. 2-Methoxy-5-methyl-1,6-bis(trifluoromethyl)naphthalene (15). A suspension of NaO₂CCF₃ (43.08 g, 0.317 mol), CuI (30.17 g, 0.158 mol), and 14 (14.5 g, 39.6 mmol) in anhydrous 1-methyl-2-pyrrolidinone (145 mL) was heated at 180 °C under a dry N₂ atmosphere for 2.5 h. The reaction was cooled to room temperature and diluted with water (1.4 L). The resultant solid was collected by suction filtration, washed with water (2 × 100 mL), and triturated with Et₂O (5 × 100 mL). The ether phase was washed with water (3 × 100 mL), brine (1 × 50 mL), dried (MgSO₄), and concentrated. The crude product was flash chromatographed (19:1 petroleum ether/EtOAc) to provide 15 as a white solid (5.94 g, 73%): mp 124–125.5 °C; NMR (CDCl₃, 200 MHz) δ 2.80 (s, 3 H, ArCH₃), 4.02 (s, 3 H, ArOCH₃), 7.41 (d, 1 H, J = 9.9 Hz, ArH), 7.71 (d, 1 H, J = 9.5 Hz, ArH), 8.13 (d, 1 H, J = 8.9 Hz, ArH), 8.35 (d, 1 H, J = 9.5 Hz, ArH); MS (m/e) 308 (51), 239 (27), 196 (32), 146 (28), 69 (100). Anal. (C₁₄H₁₀F₆O) C, H.

Method E. 2-Methoxy-5-methyl-6-nitro-1-(trifluoromethyl)naphthalene (16). To a cooled solution (0-5 °C) of Ac₂O (1.28 L) was added fuming HNO₃ (90%, specific gravity = 1.5 g/cm^3 , 320 mL) dropwise via an addition funnel at such a rate as to keep the internal temperature at or below 8 °C (1.3 h total addition time). After the internal temperature had again cooled to 3-4 °C, 11⁶ (400 g, 1.77 mol) was added portionwise such that the internal temperature did not rise above 10 °C and each portion was added after the temperature had recooled to 5 °C (addition time 1.25 h). After an additional 15 min the reaction mixture was added to water (3 L). The resulting solid was filtered, washed with water, and dried in vacuo. The dry solid (450 g, 5:1 mixture of 16/17) was recrystallized from EtOH (4.5 L) to provide 16 as long yellow needles (201 g, 40%): mp 141–142 °C; NMR (CDCl₃, 200 MHz) δ 2.84 (s, 3 H, CH₃), 4.05 (s, 3 H, OCH₃), 7.47 (d, 1 H, J = 10.0 Hz, ArH), 7.87 (d, 1 H, J = 9.9 Hz, ArH), 8.16 (dm, 1 H, ArH), 8.39 (d, 1 H, J = 10.0 Hz, ArH); MS (m/e) 285 (67), 268 (80), 266 (13), 248 (48), 240 (42), 196 (100), 146 (100). Anal. (C₁₃H₁₀F₃NO₃) C, H, N. Method E'. 2-Methoxy-5-methyl-8-nitro-1-(trifluoro-

Method E'. 2-Methoxy-5-methyl-8-nitro-1-(trifluoromethyl)naphthalene (17). Powdered 11⁶ (40.0 g, 0.167 mol) was added to mechanically stirred concentrated HNO₃ at 0-10 °C. This suspension was stirred at room temperature for 30 min and then added to water (80 mL) and filtered to provide a yellow solid. This solid was flash chromatographed (4:1 to 2:3 petroleum ether/EtOAc). Product 16 (18.8 g, 40%, $R_f = 0.22$, 4:1 petroleum ether/EtOAc) eluted first followed by 17 (21.83 g, 46%, R_f 0.12, 4:1 petroleum ether/EtOAc, yellow solid). A small portion of 17 was recrystallized from petroleum ether/EtOAcs (s, 3 H, CH₃), 4.08 (s, 3 H, OCH₃), 7.25 (d, 1 H, J = 8.1 Hz, ArH), 7.47 (d, 1 H, J = 9.6 Hz, ArH), 8.04 (d, 1 H, J = 8.1 Hz, ArH), 8.22 (d, 1 H, J = 9.6 Hz, ArH); MS (m/e) 285 (71), 266 (8), 216 (70), 201 (48), 200 (32), 195 (100). Anal. ($C_{13}H_{10}F_3NO_3$) C, H, N.

Method F. 6-Amino-2-methoxy-5-methyl-1-(trifluoromethyl)naphthalene (18). Compound 16 (125 g, 0.438 mol), EtOAc (100 mL), and 10% Pd-C (2.0 g) was hydrogenated at 20 psi. Due to the exothermic nature of the reduction, the shaker was shut off periodically to keep the temperature below 60 °C. After hydrogen uptake was completed, the reaction was filtered through Sulka Floc. The filtrate was concentrated and dried in vacuo to provide 18 as a yellow solid (107 g, 96%): mp 108-110 °C; NMR (CDCl₃, 200 MHz) δ 2.40 (s, 3 H, CH₃), 3.77 (br s, 2 H, NH₂), 3.95 (s, 3 H, OCH₃), 7.04 (d, 1 H, J = 9.7 Hz, ArH), 7.26 (d, 1 H, J = 9.5 Hz, ArH), 7.92 (dm, 1 H, ArH), 8.05 (d, 1 H, J = 9.5 Hz, ArH); IR (CHCl₃) 3510, 3420; MS (m/e) 255 (100), 234 (79), 212 (75). Anal. (C₁₃H₁₀F₃NO) C, H, N.

(79), 212 (75). Anal. (C₁₃H₁₂F₃NO) Ć, H, N. Method G. 2-Fluoro-6-methoxy-1-methyl-5-(trifluoromethyl)naphthalene (20). Pyridine (184 mL) was slowly added to HF-pyridine (558 mL) contained in a 4-L nalgene bottle at -60 °C under a dry N₂ atmosphere. Powdered 18 (152 g, 0.59 mol) was added followed by powdered NaNO₂ (68.8 g, 0.997 mol). The cooling bath was removed and the reaction was allowed to warm to room temperature. The reaction slurry was placed in an oil bath (65 °C) and heated until N_2 evolution ceased (2 h). The reaction was cooled to 10 °C and water (4 L) was added. The solid was filtered, washed with water, and dried in vacuo. The crude product (125 g) was recrystallized from ethanol to afford a light orange solid (96 g, 62%): mp 98-99 °C; NMR (CDCl₃, 200 MHz) δ 2.56 (d, 3 H, J = 2.2 Hz, CH₃), 3.99 (s, 3 H, OCH₃), 7.28 (d, 1 H, J = 9.3 Hz, ArH), 7.34 (t, 1 H, J = 9.3 Hz, ArH), 8.04(m, 1 H, ArH), 8.13 (d, 1 H, J = 9.3 Hz, ArH); MS (m/e) 258 (96). Anal. $(C_{13}H_{10}F_4O)$ C, H.

Method H. 2-Fluoro-6-methoxy-5-(trifluoromethyl)-1naphthoic Acid (25). A suspension of 20 (200 g, 0.77 mol), CCl₄ (3.1 L), NBS (151 g, 0.85 mol), and (PhCO₂)₂ (1.2 g) was heated at reflux for 4 h. The reaction slurry was cooled to 30 °C and filtered through silica gel, and the silica gel was washed with CH₂Cl₂. The organic phase was concentrated and dried in vacuo to afford 1-(bromomethyl)-2-fluoro-6-methoxy-5-(trifluoromethyl)naphthalene (266 g, 100%): mp 96–98 °C. Anal. (C₁₃-H₉BrF₄O) C, H.

This bromide (329 g, 0.87 mol), EtOH (3.3 L), HCO_2Na (145 g, 2.10 mol), and water (847 mL) were heated to reflux for 2 h. Upon cooling 2.5 N NaOH (250 mL) was added and the reaction mixture was then concentrated to a slurry. After the addition of water the solid was filtered, washed thoroughly with water, and dried in vacuo to afford 2-fluoro-1-(hydroxymethyl)-6-methoxy-5-(trifluoromethyl)naphthalene as a white solid (236 g, 99%): mp 110–113 °C (toluene/hexane). Anal. (C₁₃H₈F₄O₃) C, H. Jones reagent (518 mL) was added dropwise over 45 min to

Jones reagent (518 mL) was added dropwise over 45 min to a stirred solution of the alcohol (211 g, 0.77 mol) in acetone (2.4 L) at 10–15 °C. Stirring was continued for 2 h at ambient temperatures. The reaction slurry was cooled to 10 °C and treated with *i*PrOH (400 mL). The reaction was then filtered through Celite and the cake was washed with acetone. The filtrate was concentrated to a green solid. Water was added and the solid was mechanically stirred for 1 h. The tan solid was collected and washed thoroughly with water. The crude compound (204 g) was recrystallized from toluene/hexane to afford 25 as white crystals (158 g, 71%): mp 177–178 °C; NMR (CDCl₃, 200 MHz) δ 4.02 (s, 3 H, OCH₃), 7.40 (t, 1 H, J = 9.5 Hz, ArH), 7.46 (d, 1 H, J =9.6 Hz, ArH), 8.37 (m, 1 H, ArH), 8.53 (d, 1 H, J = 9.6 Hz, ArH); IR (KBr) 3600–2500, 1695; M_r 288.0380 (calcd for C₁₃H₃F₄O₃, 288.0409).

Method I. 2-Ethoxy-6-methoxy-5-(trifluoromethyl)naphthoic Acid (27a). Absolute EtOH (8.1 mL, 139 mmol) was added over a 5-min period to a stirred, room temperature suspension of NaH (7.3 g, 151 mmol, 50% dispersion in mineral oil) in dry THF (30 mL). After gas evolution ceased, CuI (13.2 g, 151 mmol) and a solution of 2-bromo-6-methoxy-5-(trifluoromethyl)-1-naphthoic acid (22)⁷ (4.05 g, 11.6 mmol) in dry THF (20 mL) were added slowly to avoid excessive foaming. The dark green reaction mixture was heated to reflux for 2.5 h, cooled to room temperature, and added to water (1 L). Ether (600 mL) was added and the reaction mixture was acidified with concentrated HCl and stirred for 10 min. The biphasic mixture was filtered through Celite and the Celite was washed with Et_2O (100) mL) and EtOAc (100 mL). The layers were separated, and the organic layer was washed with brine and dried $(MgSO_4)$. The solvent was removed and the gummy solid was triturated with petroleum ether. The resulting solid was dried in vacuo (2.66 g,

74%). A small portion was recrystallized from EtOH/water to give 27a as an off white solid: mp 178–180 °C; NMR (CDCl₃, 200 MHz) δ 1.52 (t, 3 H, J = 4.8 Hz, OCH₂CH₃), 3.99 (s, 3 H, OCH₃), 4.35 (q, 2 H, J = 4.8 Hz, OCH₂CH₃), 7.39 (m, 2 H, ArH), 8.34 (dm, 1 H, ArH), 8.77 (d, 1 H, ArH); IR (KBr) 3400–2700, 1710. Anal. (C₁₈H₁₃F₃O₄) C, H.

Method J. 6-Methoxy-2-(methylthio)-5-(trifluoromethyl)naphthoic Acid (28). Copper(I) oxide (0.82 g, 5.72 mmol) and KOtBu (1.28 g, 11.44 mmol) were added to a stirred solution of 22^7 (1.00 g, 2.86 mmol) in anhydrous DMF at room temperature under an Ar atmosphere. Methyl mercaptan was condensed into the reaction vessel. The reaction was heated to reflux for 3.25 h. The reaction was cooled to room temperature and diluted with 1 N HCL (200 mL) and ether (100 mL). The two-phase system was stirred rapidly for 10 min then filtered through Celite. The Celite was washed with Et_2O (4 × 30 mL). The two layers of the filtrate were separated; the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic phase was washed with brine $(2 \times 50 \text{ mL})$, dried (MgSO₄), and concentrated to provide 28 as a yellow solid (0.86 g, 95%). A small sample was recrystallized from CHCl₃/hexane for analysis: mp 208-209 °C; NMR (DMSO-d₆, 200 MHz) δ 2.55 (s, 3 H, SCH₃), 4.00 (s, 3 H, OCH₃), 7.73 (t, 2 H, J = 9.8 Hz, ArH), 8.01 (d, 1 H, J = 9.5 Hz, ArH), 8.08 (d, 1 H, J = 10.0 Hz, ArH); IR (KBr) 1680. Anal. $(C_{14}H_{11}F_3O_3S)$ C, H.

Method K. 2,6-Dimethoxy-1-naphthalenecarboxylic Acid (30). A mixture of 2,6-dimethoxy-1-naphthaldehyde (29)¹³ (21.6 g, 95.3 mmol), resorcinol (14.71 g, 134 mmol, technical), p-dioxane (95 mL), tert-butyl alcohol (95 mL), and a catalytic amount of acetic acid (10 drops) was heated gently until it became homogeneous (\sim 70 °C). Then a solution of sodium chlorite (80%, 12.94 g, 114 mmol, Aldrich technical grade), dissolved in water (38 mL) was added. The solution was stirred and allowed to cool to room temperature over 30 min. The mixture was concentrated and the residue was partitioned between CH₂Cl₂ and 1 M KOH. The KOH phase was washed with CH_2Cl_2 and acidified with 6 N HCl. The acidified aqueous phase was extracted with CH₂Cl₂. The extracts were combined, washed with brine, dried (Na₂SO₄), and concentrated to provide 30 (18.0 g, 82%) as an off white solid: mp 153-155 °C; NMR (CDCl₃, 200 MHz) δ 3.91 (s, 3 H), 4.09 (s, 3 H), 7.10 (m, 1 H), 7.24–7.35 (m, 2 H), 7.89 (d, 1 H), 8.61 (d, 1 H); IR (KBr) 3300-2900, 1690. Anal. (C₁₃H₁₂O₄) C, H.

Method M. 6-Methoxy-2-(phenylmethoxy)-1naphthalenecarboxaldehyde. 1-Propanethiol (12.8 mL, 0.141 mol) was added over a 20-min period to a suspension of NaH (97%, 2.92 g, 0.122 mol) in DMF (50 mL) at 0 °C under a dry N_2 atmosphere. To the resulting solution was added a solution of 2,6-dimethoxy-1-naphthaldehyde (29)¹³ (21.6 g, 0.100 mol) in DMF (100 mL) and the mixture was heated at 50–60 °C for 3 h. Anhydrous K₂CO₃ (28 g, 0.20 mol) and benzyl bromide (28.6 mL, 0.24 mol) were added, and heating was continued for 2 h. The reaction mixture was cooled to room temperature overnight. The mixture was concentrated and the residue was dissolved in water (800 mL) and EtOAc (1 L). The organic phase was collected, washed successively with 1 M KOH (400 mL), water (200 mL), and brine, and dried (Na_2SO_4) . The residue was recrystallized from absolute EtOH to provide the title compound as a yellow solid (19.6 g, 67%): mp 115-117 °C; NMR (CDCl₃, 200 MHz) δ 3.91 (s, 3 H), 5.31 (s, 2 H), 7.08 (d, 1 H, J = 2 Hz) 7.2-7.5 (m, 7 H), 7.95 (d, 1 H, J = 7 Hz), 9.21 (d, 1 H, J = 8 Hz), 10.94 (s, 1 H); IR (KBr) 1650. Anal. (C₁₈H₁₆O₃) C, H.

Method N. 7-Methoxynaphthol[1,2-c]furan-1(3H)-one (34). sec-Butyllithium (1.3 M in hexane, 15.06 mL, 19.58 mmol) was added over a period of 10 min to a stirred solution of 6methoxy-1-naphthoic acid diethylamide (33)¹⁷ (5.0 g, 19.0 mmol) and TMEDA (2.96 mL, 19.58 mmol) in THF (100 mL) at -78 °C under a dry N₂ atmosphere. After an additional 1 h, DMF (3.75 mL, 47.50 mmol) was added over a 10-min period. The reaction mixture was warmed to room temperature, stirred for 1 h, and quenched with 3 M HCl (29 mL). The reaction mixture was concentrated and partitioned between ether (200 mL) and water (200 mL). The ether layer was dried (brine, Na₂SO₄) and concentrated to provide N,N-diethyl-2-formyl-6-methoxy-1naphthalenecarboxamide as a colorless oil (5.10 g, 94%): NMR (CDCl₃, 400 MHz) δ 0.94 (t, 3 H, J = 7.2 Hz, CH₂CH₃), 1.41 (t, 3 H, J = 7.2 Hz, CH₂CH₃), 3.06 (dq, 2 H, J = 3.2, 7.1 Hz, CH₂), 3.76 (dq, 2 H, J = 3.6, 7.1 Hz, CH₂), 3.95 (s, 3 H, OCH₃), 7.17 (d, 1 H, J = 2.5 Hz, ArH), 7.23 (dd, 1 H, J = 2.5, 9.2 Hz, ArH), 7.78 (d, 1 H, J = 9.2 Hz, ArH), 7.79 (d, 1 H, J = 8.6 Hz, ArH), 10.14 (s, 1 H, CHO).

The amide aldehyde (5.06 g, 17.73 mmol) was dissolved in absolute EtOH (87 mL) and NaBH₄ (0.216 g, 5.7 mmol) was cautiously added at ambient temperature. After 3 h the reaction mixture was concentrated and added to a mixture of CH₂Cl₂ (650 ml) and water (430 mL). HCl (1 M) was added until the aqueous layer had acidic pH, and the layers were separated. The CH₂Cl₂ layer was dried (brine, Na₂SO₄) and concentrated to provide N,N-diethyl-2-(hydroxymethyl)-6-methoxy-1-naphthalenecarboxamide as an oil (5.10 g, 100%): NMR (CDCl₃, 200 MHz) δ 0.92 (t, 3 H, J = 7.2 Hz, CH₃), 1.36 (t, 3 H, J = 7.2 Hz, CH₃), 3.05 (q, 2 H, J = 7.2 Hz, NCH₂), 3.72 (m, 2 H, NCH₂), 3.90 (s, 3 H, OCH₃), 4.54 (d, 1 H, J = 12 Hz, CH₂OH), 4.72 (d, 1 H, J =12 Hz, CH₂OH), 7.12 (m, 2 H, ArH), 7.48 (d, 1 H, J = 9.0 Hz, ArH), 7.60 (d, 1 H, J = 9.0 Hz, ArH), 7.72 (d, 1 H, J = 9.0 Hz, ArH).

A solution of the alcohol (5.10 g, 17.73 mmol), p-toluenesulfonic acid hydrate (5.10 g, 26.81 mmol), and toluene (187 mL) were heated at reflux overnight. The solvent was removed and the residue was flash chromatographed (1:1 hexane/EtOAc) to provide 34 (2.83 g, 74%) as a white solid: mp 164–166 °C (EtOH); NMR (CDCl₃, 200 MHz) δ 3.95 (s, 3 H, OCH₃), 5.35 (s, 2 H, OCH₂), 7.25 (d, 1 H, J = 3.0 Hz, ArH), 7.37 (dd, 1 H, J = 3.0, 9.2 Hz, ArH), 7.47 (d, 1 H, J = 8.4 Hz, ArH), 8.02 (d, 1 H, J = 8.4 Hz), 8.89 (d, 1 H, J = 9.2 Hz); IR (KBr) 1740; M_r 214.0623 (calcd for C₁₃H₁₀O₃, 214.0630).

Method O. 6-Methoxy-2-methyl-1-naphthalenecarboxylic Acid (36). Propanethiol (8.64 mL, 95.3 mmol) was added dropwise to a stirred suspension of NaH (97%, 1.95 g, 78.8 mmol) in DMF (80 mL) at room temperature under a dry N₂ atmosphere. A solution of 34 (6.80 g, 31.8 mmol) in DMF (80 mL) was added and the solution was heated at 70 °C for 4.5 h. The reaction mixture was cooled to room temperature and added to 1 N HCl (400 mL). The oil that separated was extracted with toluene (400 mL). The toluene extract was washed with water (200 mL) and saturated aqueous NaHCO₃ (2×200 mL). The NaHCO₃ layer was acidified with 6 N HCl and then extracted with toluene (400 mL). The toluene layer was dried (brine, MgSO₄) and concentrated. The resulting oil was triturated with hexane and the solid was filtered and dried in vacuo to provide 6-methoxy-2-[(propylthio)methyl]-1-naphthalenecarboxylic acid as an off-white solid (4.60 g, 50%): mp 80-83 °C; NMR (CDCl₃, 200 MHz) δ 0.92 (t, $3 H, J = 7.0 Hz, CH_2CH_3), 1.57 (quin, 2 H, J = 7.0 Hz, CH_2CH_3),$ 2.45 (t, 2 H, J = 7.0 Hz, SCH₂), 3.92 (s, 3 H, OCH₃), 4.02 (s, 2 H, ArCH₂S), 7.14 (d, 1 H, J = 3.0 Hz, ArH), 7.23 (m, 2 H, ArH), 7.52 (d, 1 H, J = 9.0 Hz, ArH), 7.80 (d, 1 H, J = 9.0 Hz, ArH), 8.05 (d, 1 H, J = 9.0 Hz, ArH); IR (KBr) 3300-2300, 1680. Anal. $(C_{16}H_{18}O_3S)$ C, H.

A solution of the thioether (4.0 g, 13.8 mmol) in absolute EtOH (150 mL) was treated with Raney nickel (50% suspension in water, 88.8 g) and the suspension was stirred overnight under a dry N₂ atmosphere. The reaction mixture was filtered through Sulka Floc and the cake was washed with 9:1 EtOH/1 N NaOH (1 L). The filtrate was concentrated, acidified with 1 N HCl, and extracted with EtOAc (3×500 mL). The EtOAc phase was dried (brine, Na₂SO₄) and concentrated to provide 34 as a tan solid (2.79 g, 93%): mp 160-162 °C (6:1 MeOH/H₂O); NMR (CDCl₃, 200 MHz) δ 2.62 (s, 3 H, CH₃), 3.91 (s, 3 H, OCH₃), 7.2-7.4 (m, 3 H, ArH), 7.75 (d, 1 H, J = 9.0 Hz, ArH), 8.03 (d, 1 H, J = 9.0 Hz); IR (KBr) 3300-2300, 1685. Anal. (C₁₃H₁₂O₃) C, H.

Method P. 7-Methoxy-3-phenylnaphtho[1,2-c]furan-1-(3H)-one (35). The 2-lithio analogue of 6-methoxy-1-naphthoic acid diethylamide 33^{17} (19.0 mmol) was prepared according to method N. Benzaldehyde (2.89 mL, 28.5 mmol) was added over a 10-min period at -78 °C and the reaction mixture was warmed to room temperature for 2 h. p-Toluenesulfonic acid hydrate (9.09 g, 45.5 mmol) was added and the reaction mixture was concentrated. Toluene (150 mL) was added and the solution was heated at reflux for 3 h. The cooled reaction mixture was concentrated and flash chromatographed (gradient 3:1 to 1:1 hexane/EtOAc) to provide a solid (4.66 g, 85%) which was recrystallized from ethanol to provide 35 as a white solid (3.62 g, 66%): mp 146-148 °C; NMR (CDCl₃, 200 MHz) δ 3.97 (s, 3 H, OCH₃), 6.45 (s, 1 H, OCHPh), 7.2-7.5 (m, 8 H, ArH, PhH), 8.01 (d, 1 H, J = 8.1 Hz, ArH), 9.00 (d, 1 H, J = 9.6 Hz, ArH); IR (KBr) 1745. Anal. (C₁₉H₁₄O₃) C, H.

Method Q. 6-Methoxy-2-(phenylmethyl)-1-naphthalenecarboxylic Acid (37). A suspension of 35 (3.6 g, 12.4 mmol), 5% Pd-C (0.8 g), and glacial HOAc (45 mL) were stirred in a 95 °C oil bath under 1 atm of H₂ pressure for 4 h. The cooled reaction mixture was filtered through Sulka Floc and the cake was washed with EtOAc (400 mL). The filtrate was concentrated and dried in vacuo to provide 37 as a white solid (3.33 g, 92%): mp 145–147 °C (EtOH); NMR (CDCl₃, 200 MHz) δ 3.92 (s, 3 H, OCH₃), 4.23 (s, 2 H, CH₂), 7.2–7.5 (m, 8 H, PhH, ArH), 7.74 (d, 1 H, J = 8.7 Hz, ArH), 8.00 (d, 1 H, J = 9.2 Hz, ArH); IR (KBr) 3300–2300, 1690. Anal. (C₁₉H₁₆O₃) C, H.

Method T. α -[(3-Methoxyphenyl)methylene]benzeneacetaldehyde (42e). To a solution of anhydrous EtOH (30 mL) and KOH (2.53 g, 46.3 mmol), at 10 °C, was added 3-methoxybenzaldehyde (41) (70.0 g, 514 mmol) and the mixture was stirred for 10 min. hydrocinnamaldehyde (40e) (61.9 g, 427 mmol) was added dropwise over a 4-h period. The mixture was stirred for 2 h and placed in a refrigerator overnight, poured into H₂O, and extracted with Et₂O. The crude product was distilled (0.5 mmR 170-176 °C) to provide 42e as a light yellow oil (75 g, 65%): NMR (DMSO-d₆, 200 MHz) δ 3.63 (s, 3 H, OCH₃), 3.85 (s, 2 H, ArCH₂), 6.9-7.3 (m, 9 H, ArH, olefinic), 7.4 (s, 1 H, ArH), 9.7 (s, 1 H, CHO); IR (film) 1685; MS (m/e) 252 (62), 161 (15). Anal. (C₁₇H₁₆O₂) C, H.

Method T'. 2-Fluoro-3-(3-methoxyphenyl)-2-propenal (42a). 3-Methoxybenzaldehyde (41) (60 mL, 0.50 mol) and ethyl fluoroacetate (48 mL, 0.50 mol) were simultaneously added to a 0–5 °C cooled suspension of NaH (10.0 g, 0.5 mol), Et_2O (600 mL), and EtOH (2 mL) over a 1-h period. The resulting suspension was stirred overnight at room temperature and then added to water (300 mL). The layers were separated, and the organic phase was dried and concentrated to provide an oil which was flash chromatographed (85:15 hexanes/EtOAc) to provide 2-fluoro-3-(3-methoxyphenyl)-2-propenoic acid ethyl ester as an oil. The aqueous phase was acidified to pH 1 with concentrated HCl and extracted with ether (300 mL). The ether phase was dried (MgSO₄) and concentrated to provide the corresponding acid. This acid was esterified under Fisher conditions (concentrated $H_2SO_4/EtOH$) to provide more of the desired ethyl ester. The combined amount of the ethyl ester was distilled to provide pure product (63.4 g, 57%): bp 122 °C (0.1 mm); NMR (CDCl₃, 200 MHz) δ 1.65 (t, 3 H, J = 8 Hz, CH₂CH₃), 4.09 (s, 3 H, OCH₃), 4.63 (q, 2 H, CH₂CH₃), 7.1-7.3 (m, 2 H, vinyl H, ArH), 7.45-7.65 (m, 3 H, ArH); IR (CHCl₃) 1720.

A solution of this ester (63.4 g, 0.288 mol) in Et₂O (600 mL) was added dropwise over 2 h to a stirred suspension of LiAlH₄ (7.50 g, 0.2 mol) in Et₂O (200 mL) at 0-5 °C under a dry N₂ atmosphere. This suspension was stirred overnight at room temperature and the LiAlH₄ was destroyed by careful addition of water at 0 °C. The organic layer was separated, dried (brine, MgSO₄), and concentrated. The crude reaction product was flash chromatographed (4:1 hexanes/EtOAc) to provide 2-fluoro-3-(3-methoxyphenyl)-2-propenol as an oil (50.4 g, 96%): NMR (CDCl₃, 200 MHz) δ 4.12 (s, 3 H, OCH₃), 4.60 (d, 2 H, CH₂OH), 6.60-7.70 (m, 5 H, vinyl H, ArH); IR (CHCl₃) 3620 (sharp), 3460 (br).

A mixture of this allylic alcohol (50.0 g, 0.274 mol), MnO₂ (150 g), and ether (1 L) was stirred at room temperature for 24 h. The reaction mixture was filtered through Celite and the Celite cake was washed with ether. The combined ether extracts were concentrated, and the crude product was flash chromatographed (9:1 petroleum ether/EtOAc) to provide 42a as an oil (36.7 g, 73%): NMR (CDCl₃, 200 MHz) δ 4.04 (s, 3 H, OCH₃), 6.89 (m, 1 H, vinyl H), 7.25 (m, 2 H, ArH), 7.54 (m, 2 H, ArH), 9.89 (d, 1 H, J = 8 Hz, CHO); IR (CHCl₃) 2840, 2740, 1680.

Method U. 2-Bromo-3-(3-methoxyphenyl)-2-propenal (42b). A solution of Br₂ (13.0 g, 81.3 mmol) in glacial HOAc (80 mL) was added over a 1-h period to a stirred, cold (10 °C) solution of 3-(3-methoxyphenyl)-2-propenal 43^{30} in HOAc (80 mL). Anhydrous K₂CO₃ (13.0 g, 101 mmol) was added and the reaction mixture was slowly warmed to 100 °C for 1 h. After cooling to room temperature, the reaction mixture was poured into ice (800 g). The separated oil was extracted with Et₂O (600 mL), washed with saturated aqueous NaHCO₃ (200 mL) and dried (brine, MgSO₄). The extracts were concentrated and flash chromatographed (95:5 petroleum ether/EtOAc) to provide **42b** as an oil (8.4 g, 43%): NMR (CDCl₃, 200 MHz) δ 3.82 (s, 3 H, OCH₃), 7.04 (dd, 1 H, J = 2, 8.5 Hz, ArH), 7.40 (t, 1 H, J = 8.5 Hz, ArH), 7.53 (dd, 1 H, J = 2, 8.5 Hz, ArH), 7.64 (d, 1 H, J = 2 Hz, ArH), 7.84 (s, 1 H, olefinic), 9.30 (s, 1 H, CHO); IR (CHCl₃) 2860, 1695; MS (m/e) 242 (43), 240 (45), 214 (43), 212 (45), 133 (100). Anal. (C₁₀H₉BrO₂) C, H.

Method V. 3-(3-Methoxy-4-methylphenyl)-2-propenal (45). To a cold (0 °C) suspension of NaH (80% in mineral oil, 6.3 g, 210 mmol) in toluene (500 mL) was added triethyl phosphonoacetate (41.62 mL, 210 mmol) dropwise over a 1-h period, and the mixture was stirred for 1 h. Aldehyde 44^{21} (21.0 g, 140.0 mmol) in THF (50 mL) was added dropwise and the solution was stirred at room temperature for 20 h, quenched with H₂O, poured into H₂O, extracted with EtOAc, and dried (MgSO₄). Evaporation and purification by flash chromatography (4:1 hexane/EtOAc) gave 3-(3-methoxy-4-methylphenyl)-2-propenoic acid ethyl ester (25.0 g, 81%): mp 60-61 °C; MS (m/e) 220 (87), 175 (100). Anal. (C₁₃H₁₆O₃) C, H.

To a cold (-78 °C) solution of the ester (25.0 g, 113 mmol) in Et₂O (500 mL) was added DIBAL (1.0 M, 227.6 mL) dropwise over a 30-min period. The mixture was stirred for 1 h, quenched with MeOH, EtOAc, H₂O, acidified with HCl (6 N), extracted with EtOAc, and dried over MgSO₄. Evaporation gave an oil (18.9 g). This oil was dissolved in CH₂Cl₂ (300 mL) and to it was added PCC (27.46 g, 127.4 mmol) portionwise. After stirring for 2 h, ether (800 mL) was added and the dark suspension was filtered through a Florisil pad. Evaporation gave 45 as a yellow oil (13.9 g, 72%) which was carried to the next step without any further purification. A small sample was purified by flash chromatography (10:1 hexane/EtOAc). NMR (DMSO-d₆, 200 MHz) δ 2.18 (s, 3 H, ArCH₃), 3.85 (s, 3 H, OCH₃), 6.87 (dd, 1 H, J = 15.2 Hz, 7.8Hz, CHCHO), 7.23 (m, 2 H, ArH), 7.32 (s, 1 H, ArH), 7.72 (d, 1 H, J = 15.2 Hz, CH=CHCHO), 9.68 (d, 1 H, J = 7.8 Hz, CHO); IR (film) 1680; MS (m/e) 176 (69), 161 (100). Anal. ($C_{15}H_6O_2$) C. H.

Method X. 2-Ethoxy-5-(3-methoxyphenyl)-4-(phenylmethyl)-2,4-pentadienoic Acid Ethyl Ester (48, R = 4-CH₂Ph). To a suspension of NaH (80% in oil, 3.57 g, 119 mmol) in DMF (500 mL) at 0 °C was added dropwise triethyl 2-ethoxyphosphonoacetate²² (35.09 g, 130.9 mmol) over a 1-h period. After stirring for 2 h, aldehyde 42e (30.0 g, 119 mmol) was added dropwise over a 30-min period. The whole mixture was stirred at room temperature for 15 h, poured into H_2O , and extracted with 1:1 EtOAc/Et₂O. The crude product (52 g) was used without further purification. A small sample was purified by flash chromatography (4:1 hexane/EtOAc) to give a yellow oil. NMR $(DMSO-d_6, 200 \text{ MHz}) \delta 0.94 (t, J = 7.0 \text{ Hz}, 3 \text{ H}, OCH_2CH_3), 1.22 (t, 3 \text{ H}, J = 7.8 \text{ Hz}, OCH_2CH_3), 3.56 (m, 5 \text{ H}, OCH_3, OCH_2CH_3),$ 4.0 (s, 2 H, ArCH₂), 4.16 (q, 2 H, J = 7.0 Hz, OCH₂CH₃), 6.65 (s, 1 H, olefinic), 6.85 (m, 3 H, 1 olefinic, 2 ArH), 7.1-7.4 (m, 8 H, ArH); IR (film) 1720; MS (EI) (m/e) 366 (3), 320 (21). Anal. $C_{23}H_{26}O_4)$ C, H.

Method Y. 6-Methoxy-3-(phenylmethyl)-1-naphthalenecarboxylic Acid Ethyl Ester (49, R = 3-CH₂Ph). To a solution of the ester 48 (R = 4-CH₂Ph, 50 g, 136 mmol) in toluene (500 mL) were added *p*-toluenesulfonic acid hydrate (50.0 g, 262 mmol) and I₂ (0.5 g, 1.97 mmol). The mixture was refluxed for 1 h, poured into H₂O, and extracted with Et₂O. The organic layer was washed with aqueous NaHSO₃ and brine and dried (MgSO₄). The crude product was purified by flash chromatography (10:1 hexanes/ EtOAc) to provide the title compound as a light yellow solid (25.0 g, 66%): mp 86-87 °C; NMR (DMSO-d₆, 200 MHz) δ 1.4 (t, 3 H, J = 7.8 Hz, CH₂CH₂CH₃), 3.94 (s, 3 H, OCH₃), 4.13 (s, 2 H, ArCH₂), 4.4 (q, 2 H, J = 7.8 Hz, CH₂CH₂CH₃), 7.07 (d, 1 H, J = 1.6 Hz, ArH), 7.2-7.35 (m, 6 H, ArH), 7.64 (s, 1 H, ArH), 7.9 (d, 1 H, J = 1.6 Hz, ArH), 8.77 (d, 1 H, J = 9.4 Hz, ArH); IR (KBr) 1710; MS (EI) (m/e) 320 (100). Anal. (C₂₁H₂₀O₃) C, H.

Method Z. N-[[2-Fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-N-methylglycine (7a). Aqueous sodium hydroxide (2.5 N, 43 mL, 1.3 equiv) was added to a stirred solution of 53 (Y = CF₃, R = 2-F, 0.1 g, 8.3 mmol) in 4:1 THF/methanol (50 mL) at room temperature. After 25 min the THF/methanol was removed. Water (200 mL) was added and the aqueous solution was extracted with ether (150 mL). This ether extract was discarded. The aqueous phase was acidified to pH 1–3 with 10% aqueous HCl. The resulting white solid was collected, washed with water, and then recrystallized from ethanol/water to provide the title compound (2.48 g, 83%): mp 160–161 °C; NMR (DMSO- d_6 , 400 MHz; mixture of rotamers) δ 2.81, 3.16 (2 s, 3 H, NCH₃), 3.99, 4.02 (2 s, 3 H, OCH₃), 4.08 (d, 1 H, J = 17.2 Hz, NCH₂), 4.56 (d, 1 H, J = 17.2 Hz, CH₂), 7.62, 7.66 (2 t, 1 H, J = 8.7 Hz, ArH), 7.73, 7.77 (2 d, 1 H, J = 9.5 Hz, ArH), 8.17 (m, 1 H, ArH), 7.94, 8.22 (2 d, 1 H, J = 9.5 Hz, ArH); IR (KBr) 3600–2700, 1750, 1740; MS (m/e) 359 (19), 314 (17), 271 (100). Anal. (C₁₆H₁₃F₄NO₄) C, H, N.

Method AA. N-[[2-Fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-N-methylglycine Methyl Ester (53, Y = CF₃, R = 2-F). DMF (1.6 mL) was added over a 1-min period to a stirred, room temperature suspension of 25 (125.0 g, 0.434 mol) and (COCl)₂ (42 mL, 0.477 mol) in CH₂Cl₂ (600 mL) under a dry N₂ atmosphere. Dissolution occurred and after 1 h the reaction mixture was concentrated and the brown solid was dried in vacuo.

In a separate flask, triethylamine (170 mL, 1.22 mol) was added to a 0 °C, stirred suspension of sarcosine methyl ester hydrochloride (91.0 g, 0.651 mol) in dry THF (600 mL) under a dry N₂ atmosphere. A solution of the above acid chloride in dry THF (350 mL) was immediately added and the resulting suspension was warmed to room temperature and stirred for 30 min. The THF was removed and the reaction mixture was added to water (1.5 L) and scratched until it solidified. The solid was collected, washed well with water $(4 \times 300 \text{ mL})$ and triturated with petroleum ether $(2 \times 300 \text{ mL})$ and then ethanol $(3 \times 100 \text{ mL})$ to provide the title compound as a tan solid (126.0 g, 78%). A small portion (1.57 g) was recrystallized with hot filtration from petroleum ether/CHCl₃: mp 112.5-114 °C; NMR (CDCl₃, 200 MHz; mixture of rotamers) δ 2.90, 3.27 (2 s, 3 H, NCH₃), 3.56, 3.82 (2 s, 3 H, CO₂CH₃), 3.85 (d, 1 H, NCH₂), 3.97 (s, 3 H, OCH₃), 4.95 (d, 1 H, NCH₂), 7.3-7.5 (m, 2 H, ArH), 8.0, 8.25 (2 m, 2 H, ArH); IR (CHCl₃) 1745, 1645; MS (m/e) 373 (17), 271 (100). Anal. (C₁₇H₁₅F₄NO₄) C, H, N.

Method BB. N-[(Aminocarbonyl)methyl]-2-fluoro-6methoxy-5-(trifluoromethyl)-1-naphthalenecarboxamide (8a). A solution of 53 ($Y = CF_3$, R = 2-F, 126.0 g, 0.338 mol) in THF (410 mL)/methanol (350 mL) contained in a pressure apparatus at 0 °C was purged with ammonia gas for 1.5 h. This solution was warmed to room temperature with shaking where the internal pressure rose to 20 psi. After 3 days the reaction mixture was concentrated and the resulting brown solid was triturated with petroleum ether $(3 \times 300 \text{ mL})$, 1:1 petroleum ether/ether (300 mL), and ether $(3 \times 200 \text{ mL})$ and dried in vacuo to give the crude product (113 g, 94%). This tan solid was recrystallized from toluene (2.25 L) and dried at 90 °C under high vacuum to provide 8a as an off-white solid (98 g, 82%): mp 171-173 °C; NMR (CDCl₃, 400 MHz; product is a 7:1 mixture of rotamers, major rotamer reported first) δ 2.98, 3.32 (2 s, 3 H, NCH_3 , 4.01, 4.00 (2 s, 3 H, ArOCH₃), 4.22 (d, 1 H, J = 15.5 Hz, NCH_2CO_2 , 4.47 (d, 1 H, J = 15.5 Hz, NCH_2CO_2), 5.54 (br s, 1 H, $CONH_2$), 6.19 (br s, 1 H, $CONH_2$), 7.38 (t, 1 H, J = 9.7 Hz, ArH), 7.45 (d, 1 H, J = 9.4 Hz, ArH), 8.01, 7.90 (2 d, 1 H, J =9.4 Hz, ArH), 8.29 (q, 1 H, J = 3.2 Hz, ArH); IR (KBr) 3405, 1678, 1655; MS (m/e) 358 (6), 341 (6), 271 (100), 200 (34), 195 (30). Anal. (C₁₆H₁₄F₄N₂O₃) C, H, N.

Method DD. N-[2-[(Ethoxycarbonyl)amino]-2-oxoethyl]-2-fluoro-6-methoxy-N-methyl-5-(trifluoromethyl)-1naphthalenecarboxamide (54). A solution of (ethoxycarbonyl)-tert-butylcarbodiimide24 (0.436, 1.10 equiv) and 7a (0.838 g, 2.38 mmol) in anhydrous THF (13.5 mL) was heated to reflux under a dry N₂ atmosphere for 10 h. The reaction was cooled to room temperature and the organic solvent was removed. The solid was flash chromatographed (1:1 petroleum ether/ethyl acetate). The resultant foam was triturated with petroleum ether and dried to provide 54 as a white solid (0.567 g, 50%): mp 130-132 °C; NMR (DMSO-d₆, 400 MHz; product is a mixture of rotamers, major rotamer reported first) § 1.25, 1.08 (2 t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.79, 3.13 (2 s, 3 H, NCH_3), 4.17, 3.96 (2 q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.02, 3.99 (2 s, 3 H, $ArOCH_3$), 4.26 (d, 1 H, J = 17.5 Hz, NCH_2CO_2), 4.86 (d, 1 H, J = 17.6 Hz, NCH_2CO_2), 7.66, 7.62 (2 t, 1 H, J = 9.4 Hz, ArH), 7.80, 7.72 (2 d, 1 H, J = 9.5 Hz, ArH), 8.17 (m, 1 H, ArH), 8.31, 7.94 (2 d, 1

H, J = 9.5 Hz, ArH), 10.95, 10.51 (2 s, 1 H, NH); IR (KBr) 1760, 1718, 1647; MS (CI) m/e 431 (M + H, 100), 411 (32), 342 (53). Anal. (C₁₉H₁₈F₄N₂O₅) C, H, N. Method DD'. N-[[2-Bromo-6-methoxy-5-(trifluoro-

Method DD'. N-[[2-Bromo-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]carbamic Acid Methyl Ester (56, Y = CF₃, R = 2-Br, R' = Me). A suspension of 22 (2.0 g, 5.73 mmol), SOCl₂ (11 mL), and DMF (40 μ L) was heated with stirring at 60 °C under a dry N₂ atmosphere for 35 min. The reaction mixture was cooled to room temperature and the SOCl₂ was removed. The solid was dissolved in THF (20 mL) and this solution was added dropwise to stirred, cold (0-5 °C) NH₄OH over a 5-min period. After 15 min, water (100 mL) was added and the suspension was filtered. The solid was washed with water and dried in vacuo: NMR (DMSO-d₆, 200 MHz) δ 3.99 (s, 3 H, OCH₃), 7.88 (m, 2 H, ArH), 7.90-8.25 (m, 4 H, NH₂, 2 ArH).

This carboxamide (4.18 g, 12.01 mmol) was added to a stirred, cold (0-5 °C) suspension of NaH (50% dispersion in mineral oil, 632 mg, 13.2 mmol) in anhydrous THF (110 mL) precooled in an ice bath under a dry N2 atmosphere. The ice bath was removed and the suspension was stirred at ambient temperatures for 30 min, warmed to 40 °C, and stirred an additional 20 min. The reaction mixture was cooled to room temperature and ClCO₂CH₃ (0.93 mL, 12.01 mmol) in THF (25 mL) was added dropwise over a 10-min period. After an additional 20 min, saturated aqueous NH₄Cl (35 mL) was added. The reaction mixture was added to water (400 mL) and extracted with Et_2O (2 × 300 mL). The combined extracts were washed with saturated aqueous NaCl (300 mL). Silica gel (25 mL) was added to the Et₂O solution and the solvent was removed. The silica gel absorbate was flash chromatographed (3:2 petroleum ether/EtOAc) to provide the title compound as a white solid (2.71 g, 56%): mp 180-182 °C; NMR $(CDCl_3, 200 \text{ MHz}) \delta 3.75 (s, 3 \text{ H}, CO_2CH_3), 4.01 (s, 3 \text{ H}, OCH_3),$ 7.38 (d, 1 H, ArH), 7.68 (d, 1 H, ArH), 7.92 (d, 1 H, ArH), 8.17 (d, 1 H, ArH); IR (CDCl₃) 3400, 1770, 1700. Anal. (C₁₅H₁₁Br-F₃NO₄) C, H, N.

Method DD". N-[[3-Bromo-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]carbamic Acid Ethyl Ester (56, Y = CF₃, R = 3-Br, R' = Et). 3-Bromo-6-methoxy-5-(trifluoromethyl)-1-naphthalenecarboxylic acid amide was prepared from carboxylic acid 52b, thionyl chloride, and ammonium hydroxide according to the procedure in method DD': mp 255 °C. Anal. ($C_{12}H_9BrNO_2$) C, H, N.

A solution of this amide (3.0 g, 8.36 mmol) and oxalyl chloride (3.0 mL, 34.4 mmol) in 1,2-dichloroethane (50 mL) was heated at reflux temperature for 24 h. The cooled reaction mixture was concentrated and redissolved in benzene (50 mL). This benzene solution was added to a solution of absolute EtOH (10 mL) in benzene (10 mL) and the reaction mixture was heated at reflux temperature for 3 h and filtered hot. Crystals were collected from the cooled reaction mixture and triturated with hexane to provide the product (2.3 g, 64%): mp 230 °C dec; NMR (DMSO-d₆, 200 MHz) δ 1.21 (t, 3 H, J = 8 Hz, CH₂CH₃), 4.01 (s, 3 H, OCH₃), 4.13 (q, 2 H, J = 8 Hz, CH₂CH₃), 7.66 (d, 1 H, J = 9 Hz, ArH), 7.78 (s, 1 H, ArH), 8.05 (d, 1 H, J = 9 Hz, ArH), 8.36 (s, 1 H, ArH), 11.37 (s, 1 H, NH). Anal. (C₁₅H₁₃BrNO₄) C, H, N.

N-[[2-Fluoro-6-methoxy-5-(trifluoro-Method EE. methyl)-1-naphthalenyl]thioxomethyl]-N-methylglycine Methyl Ester (55, $Y = CF_3$, R = 2-F). A stirred suspension of 53 (CF₃, R = 2-F, 4.54 g, 12.16 mmol), Lawesson's reagent (3.0 g, 0.6 equiv), and toluene (45 mL) was heated to reflux under a dry N₂ atmosphere. Dissolution occurred. After 3 h, more Lawesson's reagent (1.83 g, 0.37 equiv) was added. After 19 h, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 . Silica gel was then added, and the solvents were removed. The silica gel absorbate was flash chromatographed (3:2 dichloromethane/petroleum ether) to provide the product (4.6 g, 97%). A small portion was triturated with hexane to provide an off white solid: mp 108.5-111 °C; NMR (CDCl₃, 200 MHz; mixture of rotamers) § 3.12 and 3.60 (2 s, 3 H, NCH₃), 3.72 and 3.88 (2 s, 3 H, CO₂CH₃), 3.99 (s, 3 H, OCH₃), 4.29 (d, 1 H, J = 16.8 Hz, NCH₂), 5.64 (d, 1 H, J = 16.8 Hz, NCH₂), 7.34 (t, 1 H, J = 9.3 Hz, ArH), 7.47 (d, 1 H, J = 9.9 Hz, ArH), 8.20 (m, 1 H, ArH), 8.27 (d, 1 H, J = 9.9 Hz, ArH); IR (CHCl₃) 1745. Anal. $(C_{17}H_{15}F_4NO_3S)$ C, H, N.

Method FF. N-[[2-Fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-N-(ethoxycarbonyl)- glycine 1,1-Dimethylethyl Ester (58, $Y = CF_3$, R = 2-F, R' =Et). Sodium hydride (80% by weight dispersion in mineral oil, 0.208 g, 6.92 mmol) was added to a stirred solution of 56 (CF_3 , R = 2-F, R' = Et, 2.26 g, 6.29 mmol) in anhydrous THF (75 mL) at room temperature under a dry N_2 atmosphere. After 45 min, tert-butyl bromoacetate (1.52 mL, 9.43 mmol) was added and the reaction was heated to 60 °C. After 1.25 h of heating, the reaction was cooled to room temperature and the THF was removed. The residue was suspended in Et₂O (150 mL), washed with water (2 \times 75 mL) and saturated aqueous NaCl (50 mL), and dried $(MgSO_4)$ and the Et₂O was removed. The crude oil was flash chromatographed (4:1 petroleum ether/EtOAc) then triturated with petroleum ether $(3 \times 30 \text{ mL})$ to provide a white powder (2.40)g, 81%): mp 81-83 °C; NMR (CDCl₃, 200 MHz) δ 0.81 (t, 3 H, J = 7.4 Hz, $CO_2CH_2CH_3$), 1.53 (s, 9 H, $CO_2C(CH_3)_3$), 3.98 (m, 5 H, ArOCH₃ and CO₂CH₂CH₃), 4.65 (br d, 2 H, NCH₂CO₂), 7.31 (t, 1 H, J = 9.5 Hz, ArH), 7.40 (d, 1 H, J = 9.5 Hz, ArH), 8.14(d, 1 H, J = 9.2 Hz, ArH), 8.23 (m, 1 H, ArH); IR (CHCl₃) 2990,1740, 1675. Anal. (C₂₂H₂₃F₄NO₆) C, H, N.

N-[[2-Fluoro-6-methoxy-5-(trifluoro-Method GG. methyl)-1-naphthalenyl]carbonyl]glycine 1,1-Dimethyl Ester (57, $Y = CF_3$, R = 2-F). Triethylamine (112 mL, 0.806 mol) was added to a stirred, 0 °C suspension of glycine, tert-butyl ester hydrochloride (60.4 g, 0.432 mol) in dry THF (35 mL) under a dry N₂ atmosphere. After 2 min, a solution of the acid chloride of 25 (0.288 mol, prepared by method AA from 83.0 g of 25) in dry THF (175 mL) was then added rapidly. After 10 min at 0 °C and 20 min at room temperature the THF was removed. Water (1 L) was added and the resulting solid was filtered, washed well with water, and dried in vacuo to provide 57 (R = 2-F) as a tan solid (111.4 g, 96%). A small portion was flash chromatographed (99:1 CHCl₃/CH₃CN) for analysis: mp 144-146 °C; NMR (CDCl₃, 400 MHz) δ 1.50 (s, 9 H, OC(CH₃)₃), 3.98 (s, 3 H, OCH₃), 4.22 (d, $2 H, J = 5.5 Hz, NHCH_2), 6.50 (m, 1 H, NHCH_2), 7.35 (m, 2 H,$ ArH), 8.25 (m, 1 H, ArH), 8.35 (d, 1 H, ArH); IR (CHCl₃) 3450, 3430, 1735, 1665. Anal. $(C_{19}H_{19}F_4NO_4)$ C, H, N.

N-[[2-Fluoro-6-methoxy-5-(trifluoro-Method HH. methyl)-1-naphthalenyl]carbonyl]-N-(methoxycarbonyl)glycine 1,1-Dimethyl Ester (58, $Y = CF_3$, R = 2-F, R' = Me). Sodium hydride (6.63 g, 0.221 mol, 80% dispersion in mineral oil) was added to a solution of 57 (R = 2-F, 73.7 g, 0.184 mol) in dry THF (495 mL) at room temperature under a dry N_2 atmosphere. The solution was heated to 55-60 °C for 45 min and then cooled to 0 °C. A solution of ClCO₂CH₃ (20.0 mL, 0.259 mmol) in dry THF (120 mL) was then added dropwise over a 30-min period. After an additional 30 min at room temperature saturated aqueous NH₄Cl (13 mL) was added, and the solvents were removed. The remaining oil was then triturated with water (1 L) followed by EtOH (100 mL) whereupon it solidified with scratching. The solid was filtered, triturated further with EtOH (100 mL, then 2×50 mL), washed with water (3×200 mL), and dried in vacuo to provide the title compound as a tan solid (69.0 g, 82%). A small portion was recrystallized from petroleum ether for analysis: mp 111-114 °C; NMR (CDCl₃, 200 MHz) δ 1.54 (s, 9 H, OC(CH₃)₃), 3.57 (s, 3 H, CO₂CH₃), 3.99 (s, 3 H, OCH₃), 4.65 (m, 2 H, NCH₂), 7.35 (m, 2 H, ArH), 8.12 (d, 1 H, ArH), 8.28 (m, 1 H, ArH); IR (neat) 1755, 1740, 1690. Anal. (C₂₁H₂₁F₄NO₆) C, H, N.

Method II. N-[[2-Fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-N-(methoxycarbonyl)glycine (9a). Compound 58 (Y = CF₃, R = 2-F, R' = Me, 208 g, 0.453 mol) was suspended in HCO₂H (1.9 L) and stirred at room temperature under a dry N_2 atmosphere. Dissolution occurred within 45 min. After 1.5 h the HCO₂H was removed and water (4.5 L) was added. The tan solid was filtered, washed well with water, and dried in vacuo to provide material of good purity (179.8 g, 98%). The material was further purified by dissolution in toluene (600 mL) followed by precipitation by the addition of hexane (300 mL). The resulting off white solid was collected and dried at 90 °C under high vacuum: mp 159.5-162 °C; NMR (DMSO-d₆, 400 MHz) δ 3.53 (s, 3 H, CO₂CH₃), 4.01 (s, 3 H, OCH₃), 4.62 (m, 1 H, NCH₂), 4.71 (m, 1 H, NCH₂), 7.63 (t, 1 H, ArH), 7.72 (d, 1 H, ArH), 8.15 (m, 2 H, ArH); IR (KBr) 3600-2450, 1765, 1695; MS (m/e) 403 (48), 271 (100). Anal. $(C_{17}H_{13}F_4NO_6)$ C, H, N.

Method JJ. N-[[2,6-Dimethoxy-5-(trifluoromethyl)-1naphthalenyl]carbonyl]-N-(methoxycarbonyl)glycine Phenylmethyl Ester (59, R = 2-OMe, R' = Me). The acid chloride of 2,6-dimethoxy-5-(trifluoromethyl)-1-naphthalene carboxylic acid 32 (3.16 g, 10.53 mL) was prepared as in method AA and reacted with glycine benzyl ester to provide N-[[2,6-dimethoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]glycine phenylmethyl ester (3.27 g, 69%). A solution of this amide ester (2.55 g, 5.70 mmol) in THF (115 mL) was cooled to -78 °C and treated with LDA (1.96 M in hexane, 3.49 mL, 6.84 mmol). After 10 min, ClCO₂CH₃ (0.66 mL, 8.55 mmol) was added over a 5-min period and the mixture was allowed to warm to room temperature. After 1.25 h the solvent was removed and the residue was dissolved in EtOAc (250 mL) and washed with 0.1 M H_3PO_4 (2 × 50 mL), water (50 mL), dried (brine, Na₂SO₄), and concentrated. The residue was flash chromatographed (CH2Cl2) to provide the title compound as a white solid (1.68 g, 58%): mp 167–168 °C; NMR (CDCl₃, 200 MHz) δ 3.50 (s, 3 H, CO₂CH₃) 3.89 (s, 3 H, OCH₃), 3.94 (s, 3 H, OCH₃), 4.6-5.1 (m, 2 H, NCH₂), 5.29 (s, 2 H, OCH₂), 7.15–7.45 (m, 7 H, ArH), 7.95 (d, 1 H, J = 9 Hz, ArH), 8.25 (m, 1 H, ArH). Anal. $(C_{25}H_{22}F_3NO_7)$ C, H, N.

4,5-Dihydro-2-(2,6-dimethoxy-1-Method LL. naphthalenyl)oxazole (62). The acid chloride of 30 (19.0 g, 51.8 mmol) was prepared according to the procedure in method AA and reacted with ethanolamine to provide 2,6-dimethoxy-N-(2hydroxyethyl)-1-naphthalenecarboxamide (21.38 g, 95%). This amide was added to SOCl₂ (64 mL) at room temperature and the solution was stirred for 1 h. The reaction mixture was concentrated and the residue was dissolved in Et_2O (2.5 L) and washed with 10% NaOH (2×1 L). The Et₂O phase was dried (brine, K_2CO_3) and concentrated to provide 62 as an off-white solid (15.30 g, 77%): mp 117.5-120 °C; NMR (CDCl₃, 200 MHz) δ 3.90 (s, 3 H, OCH₃), 3.95 (s, 3 H, OCH₃), 4.23 (t, 2 H, J = 8 Hz, CH₂), 4.52 (t, 2 H, J = 8 Hz, CH_2), 7.09 (d, 1 H, J = 3 Hz, ArH), 7.17 (dd, 1 H, J = 3, 9 Hz, ArH), 7.25 (d, 1 H, J = 9 Hz, ArH), 7.80(dd, 1 H, J = 3, 9 Hz, ArH); IR (KBr) 1665; MS (m/e) 257 (100),228 (35), 213 (40), 198 (27), 185 (30); M, 257.10534 (calcd for C₁₅H₁₅NO₃, 257.10519).

Method MM. N-(2-Acetoxyethyl)-5-bromo-2-butyl-6methoxy-1-naphthalenecarboxamide (63). n-Butyllithium (2.6 N in hexane, 10.4 mL, 27 mmol) was added dropwise over 15 min to a solution of 62 (5.79 g, 22.5 mmol) in THF (200 mL) at -42 °C (CH₃CN/dry ice) under an argon atmosphere. After 1.25 h the reaction mixture was quenched with a solution of CH_3OH (5 mL) in THF (20 mL). The reaction mixture was concentrated and the residue was dissolved in Et_2O (200 mL), washed with water (100 mL), dried (brine, K_2CO_3), and concentrated to provide an oil (6.19 g) that contained 4,5-dihydro-2-(2-butyl-6-methoxy-1naphthalenyl)oxazole and was used in the next step without further purification. This oil (6.14 g, 21.7 mmol) was dissolved in a solution of CH2Cl2 (20 mL) and CH3I (10 mL, 160 mmol) and stirred 40 h at room temperature. The reaction was concentrated and a mixture containing EtiPr2N (11.34 mL, 65.1 mmol), and HOAc (3.73 mL, 65.1 mmol) in EtOAc (130 mL) was added to it. After stirring for 3 h at room temperature this mixture was added to 1 M H₃PO₄ (100 mL) and EtOAc (100 mL). The layers were separated, and the organic phase was washed with 1 M H_3PO_4 (50 mL), H_2O (25 mL), and saturated aqueous NaHCO₃ (25 mL), dried (brine, Na₂SO₄), and concentrated. The crude product (7.7 g) was flash chromatographed (gradient 20:1 to 10:1 CH₂Cl₂/EtOAc) to provide N-(2-acetoxyethyl)-N-methyl-2-butyl-6-methoxy-1-naphthalenecarboxamide (3.62 g, 45% from 62) as a pale yellow oil: NMR (CDCl₃, 200 MHz, mixture of rotomers) δ 0.94 (t, 3 H, J = 7.5 Hz, CH₂CH₃), 1.2-1.8 (m, 4 H, CH₂- $(CH_2)_2CH_3$, 1.91, 2.14 (2 s, 3 H, COCH₃), 2.63 (m, 2 H, CH₂-(CH₂)₂CH₃), 2.79, 3.28 (2 s, 3 H, NCH₃), 3.92 (s, 3 H, OCH₃), 3.95 (m, 2 H, NCH₂), 4.47 (m, 2 H, OCH₂), 7.15 (m, 2 H, ArH), 7.36 (d, 1 H, J = 9 Hz, ArH), 7.56 (m, 1 H, ArH), 7.70 (d, 1 H, J = 9 Hz, ArH).

This compound was brominated with Br₂ in HOAc according to the procedure in method A to provide a light yellow solid (4.31 g) which was recrystallized from hexane/toluene to provide **63** as a tan solid (2.78 g, 64%): mp 103-105 °C; NMR (CDCl₃, 200 MHz) δ 0.92 (t, 3 H, J = 7.0 Hz, CH₂CH₃), 1.40 (m, 2 H, CH₂-(CH₂)₂CH₃), 1.65 (m, 2 H, CH₂(CH₂)₂CH₃), 2.11 (s, 3 H, COCH₃), 2.67 (m, 2 H, CH₂(CH₂)₂CH₃), 2.75 (s, 3 H, NCH₃), 3.95 (m, 2 H, NCH₂), 4.01 (s, 3 H, OCH₃), 4.46 (m, 2 H, CH₂O), 7.25 (m, 2 H, ArH), 7.46 (d, 1 H, J = 9 Hz, ArH), 7.67 (d, 1 H, J = 9 Hz, ArH), 8.19 (d, 1 H, J = 9 Hz, ArH); IR (KBr) 1735, 1630. Anal. (C₂₁H₂₆BrNO₄) C, H, N.

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Registry No. 2, 84533-47-1; 3, 84533-26-6; 4, 121731-13-3; 5a, 124323-53-1; 5b, 124323-64-4; 5c, 134057-50-4; 5d, 124323-58-6; 5e, 134057-51-5; 5f, 124323-67-7; 5g, 124323-59-7; 5h, 134057-52-6; 5i, 134057-53-7; 5j, 134057-54-8; 5k, 134057-55-9; 5l, 134057-56-0; 5m, 134057-57-1; 5n, 134057-58-2; 5o, 134057-59-3; 5p, 134057-60-6; 6a, 124323-51-9; 6b, 134057-61-7; 7a, 124323-52-0; 7b, 124323-55-3; 7c, 124323-63-3; 7d, 134057-62-8; 7e, 124323-66-6; 7f, 124323-60-0; 7g, 124323-61-1; 7h, 124323-65-5; 7i, 124323-62-2; 7j, 134057-63-9; 7k, 124323-56-4; 7l, 134057-64-0; 7m, 134057-65-1; 7n, 134057-66-2; 70, 134057-67-3; 7p, 134057-68-4; 7q, 134057-69-5; 7r, 134057-70-8; 7s, 134057-71-9; 7t, 134057-72-0; 7u, 134057-73-1; 7v, 134057-74-2; 7w, 134057-75-3; 8a, 124323-49-5; 8b, 124323-54-2; 8c, 124323-57-5; 8d, 134057-76-4; 8e, 134057-77-5; 8f, 134057-78-6; 9a, 122670-49-9; 9b, 122670-52-4; 9c, 122670-53-5; 9d, 134057-79-7; 9e, 122670-54-6; 10a, 122670-51-3; 10b, 122670-56-8; 10c, 122670-87-5; 10d, 122670-55-7; 10e, 134057-80-0; 11, 85674-78-8; 12, 122670-67-1; 13, 122670-68-2; 14, 134057-81-1; 15, 134057-82-2; 16, 122670-70-6; 17, 134057-83-3; 18, 122670-71-7; 19, 134057-84-4; 20, 122670-69-3; 21, 134057-85-5; 22, 122670-62-6; 22 carboxamide derivative, 122670-76-2; 23, 122670-65-9; 24, 134057-86-6; 25, 122670-89-7; 26, 134057-87-7; 27a, 124323-74-6; 27b, 124323-75-7; 27c, 124323-82-6; 27d, 124323-77-9; 27e, 122670-60-4; 28, 134057-88-8; 29, 55218-08-1; 30, 125342-90-7; 31, 134057-89-9; 32, 134057-90-2; 33, 114326-25-9; 34, 134057-91-3; 35, 134057-92-4; 36, 134057-93-5; 37, 134057-94-6; 38, 76283-09-5; 39, 134057-95-7; 40e, 104-53-0; 40f, 134057-96-8; 41, 591-31-1; 42a, 134057-97-9; 42b, 134057-98-0; 43, 39677-52-6; 44, 24973-22-6; 45, 134057-99-1; 48 (R = $4-CH_2Ph$), $134058-00-7; 49 (R = 3-CH_2Ph), 134058-01-8; 53, 124323-68-8; 54,$ 124323-50-8; 55 (Y = CF₃, R = 2-F), 124323-69-9; 56 (Y = CF₃, R = 2-Br, R' = Me), 122670-77-3; 56 (Y = CF₃, R = 3-Br, R' =Et), 134058-02-9; 56 (Y = CF₃, R = 2-F, R' = Et), 122670-72-8; 57 (Y = CF₃, R = 2-F), 122670-88-6; 58 (Y = CF₃, R = 2-F, R' = Et), 122670-73-9; **58** (Y = CF₃, R = 2-F, R' = Me), 122670-57-9; **59** (Y = CF₃, R = 2-OMe, R' = Me), 134058-03-0; **60**, 122670-50-2; 134058-04-1; (EtO), POCH(OEt)CO, Et, 13676-06-7; 61. (EtO)₂POCH₂CO₂Et, 867-13-0; methyl mercaptan, 74-93-1; 6methoxy-2-(phenylmethoxy)-1-naphthalenecarboraldehyde, 125342-95-2; 1-propanethiol, 107-03-9; N,N-diethyl-2-formyl-6methoxy-1-naphthalenecarbonamide, 134058-05-2; N,N-diethyl-2-(hydroxymethyl)-6-methoxy-1-naphthalenecarbonamide, 134058-06-3; 6-methoxy-2-[(propylthio)methyl]-1-naphthalenecarboxylic acid, 134077-95-5; ethyl fluoroacetate, 459-72-3; 2-fluoro-3-(3-methoxyphenyl)-2-propenoic acid ethyl ester, 120781-19-3; 2-fluoro-3-(3-methoxyphenyl)-2-propenol, 134058-07-4; 3-(3-methoxy-4-methylphenyl)-2-propenoic acid ethyl ester, 134058-08-5; 3-bromo-6-methoxy-5-(trifluoromethyl)-1naphthalenecarboxylic acid amide, 134058-09-6; aldose reductase, 9028-31-3; galactinol, 3687-64-7.